Specification

Heteroaryl carbamoyl benzene derivatives.

The Field of Technology

This invention relates to the following, namely, the glucokinase activator which is containing as effective ingredient heteroaryl carbamoyl benzene derivatives. Moreover, it is related to novel heteroaryl carbamoyl benzene derivatives.

Background Technique

Glucokinase (GK) (ATP : D-hexose 6-phosphotransferase, EC2.7.1.1) is one of four kinds of mammalian hexokinases (hexokinase IV). Hexokinase is an enzyme that catalyses the reaction of the first stage of the glycolytic pathway from glucose to glucose 6 phosphate. Glucokinase expression is mainly localised in liver and pancreatic β cells, and by controlling th erate-limiting step of glucose metabolism in these cells it has an important role in glucose metabolism of the whole body. The glucokinase of liver and pancreatic β cells have respectively different sequences of the N terminal 15 amino acids due to different splicing, but their enzymatic characteristics are the same. In the three hexokinases (I, II, III) other than the glucokinase, the enzyme activity is saturated at glucose concentration of 0.1 mM or less, whereas, the Km with respect to glucose of glucokinase is at 8 mM which is close to the physiological blood glucose level. Accordingly, facilitation of intracellular glucose metabolism occurs via glucokinase in response to the blood glucose change from the normal blood sugar (5 mM) to postprandial blood glucose rise (10-15 mM).

About 10 years ago, a hypothesis was proposed that the glucokinase works as a glucose sensor in pancreatic β cells and liver (for example Garfinkel D et al, 'Computer modeling identifies glucokinase as glucose sensor of Pancreatic β-cells', American Journal Physiology, Vol 247, (3Pt2) 1984, pp. 527-536).

In practice, it is clear from results of a recent glucokinase genetically modified mouse, that glucokinase, carries out an important role in glucose homeostasis of whole body. The mouse whose glucokinase gene is destroyed dies soon after birth (for example Grupe A et al., 'Transgenic Knockouts reveal a critical requirement for pancreatic β cell glucokinase in maintaining glucose homeostasis', Cell, Vol 83, 1995, p69-78), while on the other hand, for normal and diabetes mellitus mice which overexpressed glucokinase, the blood glucose level becomes low (for example Ferre T et al. 'Correction of diabetic alterations by glucokinase', Proceedings of the National Academy of Sciences of the U.S.A, vol 93, 1996, p7225-7230). Although the reaction of hepatocytes is different from

pancreatic β cells when glucose concentration rises, but both cells correspond in the direction to lower the blood glucose. Pancreaic β cells start to secrete more insulin, the liver takes up more glucose and stores it as glycogen, and at the same time, decreases the sugar release.

In this way fluctuation of glucokinase enzyme activity is carrying out important role in glucose homeostasis of mammal through liver and pancreas β cells. A mutation of glucokinase gene has been discovered in the cases of diabetes mellitus that occurs in youth, known as MODY2 (maturity-onset diabetes of the young), and the reuction of glucokinase activity causes a blood glucose rise (for example Vionnet N et al., 'Nonsense mutation in the glucokinase gene cause early-onset non-Insulin-dependent diabetes mellitus' Nature Genetics, Vol 356, 1992 pp. 721-722).

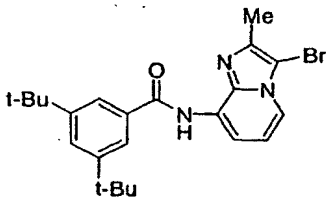
On the other hand, the lineage having mutation which causes an increase in glucokinase activity is also found, and such persons show hypoglycemic symptoms (for example Glaser B, 'Familial hyperinsulinism caused by an activating glucokinase mutation', New England Journal Medicine, Vol 338, 1998, pp. 226-230).

From these, glucokinase also plays an important role in glucose homeostasis in humans, by acting as a glucose sensor. On the other hand, blood glucose regulation using glucokinase sensor system is regarded as possible in many type II diabetics. Because insulin secretion promotion action of pancreatic β cells and enhanced sugar uptake and sugar release suppression action in liver are expected, it is regarded as useful as therapeutic drug of type II diabetes.

Recently, it has been discovered that pancreas β cell type glucokinase was expressed in rat brain, especially localised in the feeding centre (Ventromedial hypothalamus, VMH). About 20 % of the neurons of VMH, called glucose responsive neurons, has been considered in the prior art as having an important role in body weight control. Overeating occurs when glucose metabolism is suppressed by glucose analogue glucosamine intracerebral administration, in contract to the reduction of food intake when glucose is administered to rat brain. From electrophysiological experiments, it is observed that glucose responsive neurons are activated in response to physiological glucose concentration change (5-20 mM), but activity is suppressed when glucose metabolism is inhibited with glucosamine and the like. It is assumed that the mechanism in glucose concentration sensitive system of VHM is through glucokinase as it is for insulin secretion of pancreatic β cells. Accordingly, there is a possibility that the substances which can activate glucokinase of VHM in addition to liver and pancreatic β cells can correct the problem of obesity in many type II diabetics in addition to blood glucose correction effect.

From the aforesaid description, the compound which has glucokinase activation action is useful as therapeutic agent and/or preventative agent of diabetes, or therapeutic agent and/or preventative agent of chronic complication of diabetes mellitus such as retinopathy, nephropathy, neuropathy, ischemic heart disease, arteriosclerosis or the like, further as therapeutic agent and/or preventative agent of obesity.

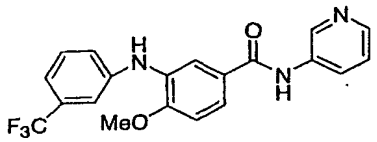
The compound represented by following (IV)



(IV)

is described as a compound having substituent in the 3 position and 5 position of the benzene ring, the same as the heteroaryl carbamoyl benzene (I) in accordance with this invention. This compound has tert-butyl groups in position 3 and 5 of the heteroaryl carbamoyl benzene ring, but there is not a case that the compound of this invention has alkyl group in both positions 3 and 5. Moreover, it has an imidazo-[1,2-a] pyridine bonded to nitrogen atom of carbamoyl group, but the relative positional relation of the position of the N of the carbamoyl group to the N included in the pyridine ring of said imidazo-[1,2-a] pyridyl group is different to the relative positions of the nitrogen atoms in the carbamoyl group and the heteroaryl group in the compounds of this invention (for example Kohyo 11-505524).

Moreover, the compound represented by following formula (V)



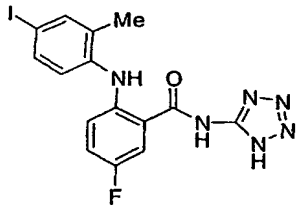
(V)

is described as the compound as the heteroaryl carbamoyl benzene having two substituents on benzene ring, (for example Kokai 2001-526255).

The compound described in the aforesaid patent literature 2 has two substituents, and one of these is a

trifluoromethylphenylamino group; and the said trifluoromethylphenylamino group corresponds to the partial structure of the compound according to the invention which includes it in the X1-A ring –R, and includes a pyridine ring as a group which bonds to the nitrogen atom of the carbamoyl group. However, the compound according to the said patent literature 2 is different in the point where the nitrogen atom of the carbamoyl group is bonded to a carbon atom in the pyridine ring bonding to the nitrogen atom of the pyridine ring and another carbon atom, whereas in the compound in accordance with this invention, the nitrogen atom of the pyridine ring bonding to the nitrogen atom of the carbamoyl group is positiond adjacent to the carbon atom in the pyridine ring bonding to the nitrogen atom of the pyridine ring. Moreover, the bonding position of methoxy group is different from bond position of the compound in accordance with this invention.

The compound represented by formula (VI)



(VI)

is described (for example JP Kohyo 2002-509536).

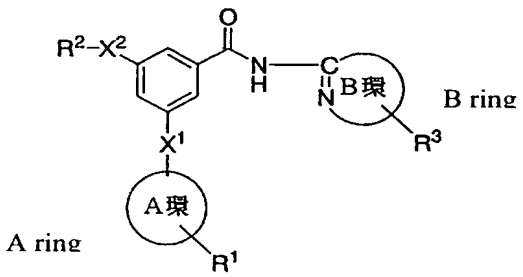
The compound described in the aforesaid patent literature 3 is in common with the compound according to the invention in a sense that it has a 2-methyl-4-iodo-phenylamino group as one of two substituents on benzene ring, and the nitrogen atom of the carbamoyl is bonded to the carbon atom adjacent to the nitrogen atom. However, the relative positions of said 2-methyl-4-iodo-phenylamino group and carbamoyl group are different, and moreover the other of the two substituents on benzene is a fluoro group, while the compound in accordance with this invention is different in that a halogen atom is not contained in a substituent on benzene ring.

Disclosure of the Invention

These inventors performed assiduous investigations in order to develop the novel diabetes mellitus drug which has a different action to the aforesaid existing agent and drug efficacy to exceed preexisting diabetes mellitus drug and as a result discovered that the compound represented by formula (I) had glucokinase activation action. This invention was completed based on this discovery.

In other words, this invention is

(1) A compound of formula (I)

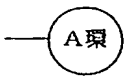


(I)

or pharmacologically acceptable salts thereof

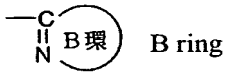
[wherein, X1 denotes an oxygen atom, sulfur atom or NH, and X2 denotes oxygen atom, sulfur atom or CH_2, R1 denotes one or two substituents that may be present on the ring A selected from the group comprising alkylsulfonyl group, alkanoyl group, lower alkyl group, hydroxyalkyl group, hydroxy group, alkylcarbamoyl group, alkyl sulphamoyl group, dialkyl sulphamoyl group, alkylthio group, alkoxy group, dialkyl carbamoyl group, alkoxycarbonylamino group, alkoxycarbonyl group, halogen atom, alkanoyl amino alkyl group, alkoxycarbonylamino alkyl group, alkylsulfonyl amino alkyl group, cyano group and trifluoromethyl group. R2 denotes straight chain or branched lower alkenyl group or lower alkyl group, or 3-7C cyclic alkyl group (wherein 1 carbon atom among the carbon atoms composing said ring (except the carbon atom bonded to X2) may be replaced with oxygen atom, NH, N-alkanoyl group or CONH), that may have substituents selected from the group comprising halogen atom, carboxyl group, alkoxycarbonyl group, hydroxy group, amino group (also said amino group may be substituted by one or two alkanoyl group or lower alkyl group), alkoxy group and N-alkylcarbamoyl group. R3 denotes one or two substituents that may be present on B ring selected from the group comprising the lower alkyl group, alkoxy group, alkylamino group, lower dialkylamino group, halogen atom, trifluoromethyl group, hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be substituted by lower alkyl group), amino alkyl group, alkanoyl group, carboxyl group, alkoxycarbonyl group and cyano group.

The formula (II)



(II)

denotes an aryl group of 6-10 members or a heteroaryl group of 5-7 members, which may have 1 or 2 substituents represented by the aforesaid R1 in ring,
and the formula (III)



B ring

(III)

denotes a monocyclic or bicyclic heteroaryl ring where the carbon atom in the B ring which is bonded to the nitrogen atom of the amide group of formula (I) forms C=N with a nitrogen atom in said ring].

(2) A compound in accordance with aforesaid (1) or pharmacologically acceptable salts thereof, wherein X1 is O or S and X2 is O or CH2.

(3) A compound in accordance with aforesaid (2) or pharmacologically acceptable salts thereof, wherein the A ring is phenyl group or 5-6 membered heteroaryl group.

(4) A compound in accordance with aforesaid (2), wherein the A ring is phenyl group.

(5) A compound in accordance with aforesaid (2), wherein the A ring is 5 to 6 membered heteroaryl group.

(6) A compound in accordance with any of aforesaid (4) or (5) or pharmacologically acceptable salts thereof, wherein R1 is alkylsulfonyl group, alkanoyl group, hydroxyalkyl group, alkylcarbamoyl group, alkyl sulphamoyl group, dialkyl sulphamoyl group, dialkyl carbamoyl group, alkoxycarbonylamino group, halogen atom, alkanoyl amino alkyl group, alkylsulfonyl amino alkyl group, alkoxycarbonylamino alkyl group.

(7) A compound in accordance with aforesaid (4) or pharmacologically acceptable salts thereof, wherein the R1 is alkylsulfonyl group, alkanoyl group, hydroxyalkyl group, alkanoyl amino alkyl group, alkylsulfonyl amino alkyl group, alkoxycarbonylamino alkyl group.

(8) A compound or pharmacologically acceptable salts thereof in accordance with aforesaid (4), wherein the R1 is alkylsulfonyl group, alkanoyl group, hydroxyalkyl group.

(9) A compound in accordance with any of aforesaid (3) – (8) or pharmacologically acceptable salts thereof, wherein the monocyclic or bicyclic heteroaryl ring where the carbon atom in the B ring which is bonded to the nitrogen atom of the amide group of formula (I) forms C=N with a nitrogen atom in said ring and which may have 1 or 2 substituents represented by the aforesaid R3 in said ring, (except the case that said heteroaryl group is 5-alkoxycarbonyl-pyridin-2-yl group or 5-carboxyl-pyridin-2-yl group).

(10) A compound in accordance with aforesaid (7) or pharmacologically acceptable salts thereof, wherein the B ring has at least one heteroatom selected from the group comprising nitrogen atom, sulfur atom and oxygen atom, in addition to the nitrogen atom forming C=N with carbon atom in said ring bonded with nitrogen atom of amide group of the said formula (I).

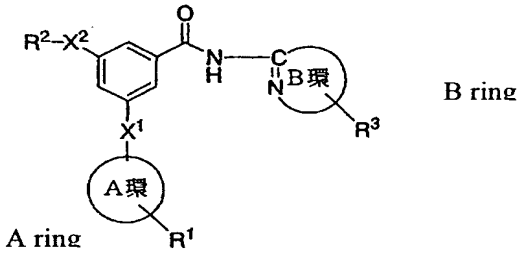
(11) A compound in accordance with any of aforesaid (1) – (10) or pharmacologically acceptable salts th)eof, wherein R2 is 3-7C cyclic alkyl group (1 of carbon atom composing said ring may be substituted by oxygen atom, NH or N-alkanoyl group), straight or branched chain lower alkyl group or lower alkenyl group, which may be substituted by halogen atom, carboxyl group, alkoxycarbonyl group, hydroxy group, amino group (also said amino group may be substituted by lower alkyl group of 1 or 2), alkoxy group, N-alkylcarbamoyl group or alkanoyl amino group.

(12) A compound in accordance with any of aforesaid (1) – (11) or pharmacologically acceptable salts thereof, wherein the B ring is thiazolyl group, imidazolyl group, isothiazolyl group, thiadiazolyl group, triazolyl group, oxazolyl group, isoxazolyl group, pyrazinyl group, pyridazinyl group, pyrazolyl group, pyrimidinyl group, pyrido thiazolyl group or benzothiazolyl group.

(13) A compound in accordance with any of aforesaid (1) – (12) or pharmacologically acceptable salts thereof, wherein R3 is lower alkyl group, alkoxy group, halogen atom, hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be substituted by lower alkyl group), amino alkyl group or alkanoyl group.

(14) A compound in accordance with any of aforesaid (1) – (12) or pharmacologically acceptable salts thereof, wherein R3 is lower alkyl group, hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be substituted by lower alkyl group).

(15) The compound which is represented Formula (I)



(I)

(wherein, each symbol has the same the aforesaid definition) is

5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-(4-methylthiazol-2-yl)-benzamide;

5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide;

5-ethoxy-3-(4-methanesulphonylphenoxy)-N-(4-methoxymethyl-thiazol-2-yl) benzamide,

5-cyclopentyloxy-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide,

3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yloxy)-N-thiazol-2-yl-benzamide,

3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide,

3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methoxymethyl-ethoxy)-N-thiazol-2-yl-benzamide,

3-(2-fluoro-4-methanesulphonylphenoxy)-5-isopropoxy-N-thiazol-2-yl-benzamide,

3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-N-(4-methyl-thiazol-2-yl)-benzamide,

5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-pyrazol-3-yl-benzamide,

5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-pyrazin-2-yl-benzamide,

3-(4-methanesulphonylphenoxy)-5-(3-methoxy-1-methyl-propoxy)-N-thiazol-2-yl-benzamide,

5-(3-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide,

5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-pyrimidin-4-yl-benzamide,

5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-(pyrimidin-2-yl)-benzamide,

N-(4-hydroxymethyl-thiazol-2-yl)-5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzamide,

N-(isoxazol-3-yl)-3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-benzamide,

3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-N-[1,3,4] thiadiazol-2-yl-benzamide,

5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(4-methyl-thiazol-2-yl)-benzamide,

N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-benzamide,

5-(2-amino-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide,

5-(2-dimethylamino-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide,

5-(2-hydroxy-propoxy)-3-(4-methanesulphonylphenoxy)-N-(4-methyl-thiazol-2-yl)-benzamide,

3-(4-methanesulphonylphenoxy)-5-(2-methoxy-propoxy)-N-(4-methyl-thiazol-2-yl)-benzamide,

5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-(thiazolo [5,4-b] pyridin-2-yl)-benzamide,

5-(2-hydroxymethyl-allyl)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazolo [5,4-b] pyridin-2-yl-benzamide,
5-(3-hydroxy-2-methyl-propyl)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide,
3-(4-methanesulphonylphenoxy)-N-(4-methyl-thiazol-2-yl)-5-(piperidine-4-yl-oxy)benzamide hydrochloride,
5-(1-acetyl-piperidine-4-yloxy)-3-(4-methanesulphonylphenoxy)-N-(4-methyl-thiazol-2-yl)-benzamide,
2-[3-(4-methanesulphonylphenoxy)-5-(4-methyl-thiazol-2-yl-carbamoyl)-phenoxy] propionic acid,
5-(3-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide,
3-(4-methanesulphonylphenoxy)-5-(1-methylcarbamoyl-ethoxy)-N-(4-methyl-thiazol-2-yl)-benzamide,
5-(2-acetylamino-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide,
N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-pyridin-2-yl-benzamide,
5-(2-hydroxy-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide,
5-(2-hydroxy-cyclopentyloxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide,
N-(4-acetyl-thiazol-2-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-benzamide,
N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-benzamide,
3-(3-fluoro-4-methanesulphonylphenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(5-methyl-thiazol-2-yl) benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-([1,2,4] thiadiazol-5-yl)-benzamide,
N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(5-methoxycarbonyl-pyridin-2-yl)-benzamide,
6-[5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzoylamino] nicotinic acid,
5-(2-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl)-3-(4-methanesulphonylphenoxy)-benzamide,
N-(5-hydroxymethyl-thiazol-2-yl)-5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzamide,
N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-

ethoxy)-benzamide,
N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(2-methylthiazol-4-yl)-benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(4-methoxymethyl-thiazol-2-yl)-benzamide,
N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide,
N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide,
N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide,
N-(2,5-dimethylthiazol-4-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-benzamide,
5-isopropoxy-3-(4-methoxycarbonylaminomethylphenoxy)-N-thiazol-2-yl-benzamide,
5-isopropoxy-3-(4-methylcarbamoyl-phenoxy)-N-thiazol-2-yl-benzamide,
3-(4-dimethylcarbamoyl-phenoxy)-5-isopropoxy-N-thiazol-2-yl-benzamide,
5-isopropoxy-3-(4-methylcarbonylaminomethyl-phenoxy)-N-thiazol-2-yl-benzamide,
5-isopropoxy-3-(4-methanesulphonylaminomethyl-phenoxy)-N-thiazol-2-yl-benzamide,
3-[4-(1-hydroxy-propyl)-phenoxy]-5-isopropoxy-N-thiazol-2-yl-benzamide,
6-[3-isopropoxy-5-(thiazol-2-yl carbamoyl)-phenoxy]-nicotinic acid methyl ester,
3-(5-hydroxymethyl-pyridin-2-yl-oxy)-5-isopropoxy-N-thiazol-2-yl-benzamide,
5-isopropoxy-3-(5-methanesulphonylpyridin-2-yl)-N-thiazol-2-yl-benzamide,
3-(5-acetyl-pyridin-2-yl-oxy)-5-isopropoxy-N-thiazol-2-yl-benzamide,
5-isopropoxy-3-(5-methoxycarbonyl-pyrazin-2-yl-oxy)-N-thiazol-2-yl-benzamide,
3-(5-cyano-pyridin-2-yl-oxy)-5-isopropoxy-N-thiazol-2-yl-benzamide,
5-isopropoxy-3-(2-oxo-1,2-dihydro-pyridin-4-yl-oxy)-N-thiazol-2-yl-benzamide,
5-isopropoxy-3-(2-oxo-1,2-dihydro-pyridin-3-yl-oxy)-N-thiazol-2-yl-benzamide,
5-isopropoxy-3-(2-oxo-1,2-dihydro-pyridin-3-yl-oxy)-N-thiazolo [5,4-b] pyridin-2-yl-benzamide,
5-isopropoxy-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazolo [5,4-b]-pyridine-2 yl-benzamide,
5-isopropoxy-3-(4-methyl-[1,2,4] triazol-3-yl sulphanyl)-N-thiazol-2-yl-benzamide,
5-isopropoxy-3-thiazol-2-yl sulphanyl-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(4H-[1,2,4] triazol-3-yl sulphanyl)-N-thiazol-2-yl-benzamide,
5-isopropoxy-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide,
5-isopropoxy-3-(5-methyl sulphanyl-[1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide,

5-isopropoxy-3-(5-methyl-[1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide,
5-(tetrahydrofuran-3-yl-oxy)-N-thiazol-2-yl-3-(4H-[1,2,4] triazol-3-yl sulphanyl)-benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-N-(4-methyl-thiazol-2-yl)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-benzamide,
5-(3-hydroxy-1-methyl-propoxy)-N-(4-methyl-thiazol-2-yl)-3-([1,3,4] thiadiazolyl-2-yl sulphanyl)-benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenyl sulphanyl)-N-thiazol-2-yl-benzamide,
3-(3-fluoro-phenylthio)-5-(2-hydroxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(pyridin-4-yl sulphanyl)-N-thiazol-2-yl-benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methyl-pyridin-3-yl sulphanyl)-N-thiazol-2-yl-benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(3-methyl-[1,2,4]-thiadiazol-5-yl)-benzamide,
N-[3-hydroxymethyl-1,2,4-thiadiazol-5-yl]-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy) benzamide,
5-(3-hydroxy-1-methyl ethoxy)-3-(4-methanesulphonylphenoxy)-N-[5-methyl-1,2,4-thiadiazol-3-yl] benzamide,
5-(hydroxy-1-methyl ethoxy)-3-(4-methanesulphonylphenoxy)-N-(3-methoxy-1,2,4-thiadiazol-5-yl) benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(1,2,5-thiadiazol-3-yl) benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(4-trifluoromethyl-thiazol-2-yl) benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(4,5,6,7-tetrahydrobenzo thiazol-2-yl) benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(pyridazin-3-yl)-benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-N-(3-isopropyl-[1,2,4]-triazol-5-yl)-3-(4-methanesulphonylphenoxy) benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(3-methyl-[1,2,4]-oxadiazol-5-yl) benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-N-[4-(1-hydroxy-1-methyl-methyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy) benzamide,
N-(4-cyano-thiazol-2-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy) benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,
5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(pyridin-2-yl) benzamide,

5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(5-methyl-isothiazol-3-yl) benzamide,
5-(3-hydroxy-cyclopentyloxy)-3-(4-methanesulphonylphenoxy)-N-(thiazol-2-yl) benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(5-methoxy-thiazol-2-yl) benzamide,
5-(1-hydroxymethyl-2-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(thiazol-2-yl) benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(1H-[1,2,3] triazol-4-yl) benzamide,
N-(1-acetyl-1H-pyrazol-3-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy) benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(pyrazol-3-yl) benzamide,
N-(5,6-dihydro-4H-cyclopenta thiazol-2-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy) benzamide,
5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(thieno [3,2-d] thiazol-2-yl) benzamide,
3-(3-fluoro-4-methanesulphonylphenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,
3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-N-(pyrazol-3-yl) benzamide,
3-(4-cyano-phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,
3-(4-ethylsulfonyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,
3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,
5-(3-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,
3-(4-ethanesulphonyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl) benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(4-isopropyl sulfonyl phenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-N-(4-hydroxy-4-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta thiazol-2-yl)-3-(4-methanesulphonylphenoxy) benzamide,
3-(4-dimethylcarbamoyl-phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,
3-(4-acetyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,

5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(1,3,4-thiadiazol-2-yl sulphanyl) benzamide,

N-(1-ethyl-1H-pyrazol-3-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy) benzamide,

5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,

5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methoxycarbonylamino methyl-phenoxy)-N-(3-methyl-1,2,4-thiadiazol-5-yl) benzamide,

5-(1-hydroxymethyl-propoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,

3-(6-methanesulphonylpyridin-3-yloxy)-5-(1-methoxymethyl-propoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,

5-isopropoxy-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,

3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl) benzamide,

5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenyl sulphanyl)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,

5-cyclopropyl oxy-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,

3-(6-methanesulphonylpyridin-3-yloxy)-5-(1-methoxymethyl-propoxy)-N-(pyrazol-3-yl) benzamide,

5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,

3-(6-ethanesulphonylpyridin-3-yloxy)-5-(1-hydroxymethyl-propoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,

5-(6-ethanesulphonylpyridin-3-yloxy)-3-(2-methoxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,

2-[3-(4-methanesulphonylphenoxy)-5-(1-methyl-1H-pyrazol-3-yl carbamoyl)-phenoxy] propionic acid tert-butyl ester,

3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-methoxy-1-methyl-ethoxy)-N-(pyrazol-3-yl)-benzamide,

3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl)-5-(tetrahydrofuran-3-yl) benzamide,

N-(1-ethyl-1H-pyrazol-3-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy) benzamide,

5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(pyrazol-3-yl) benzamide,

3-(6-methanesulphonylpyridin-3-yloxy)-5-(2-methoxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,
3-(6-ethanesulfonylpyridin-3-yloxy)-5-(2-fluoro-1-fluoromethyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,
2-[3-(4-methanesulphonylphenoxy)-5-(1-methyl-1H-pyrazol-3-yl carbamoyl)-phenoxy] propionic acid,
3-(6-ethanesulphonylpyridin-3-yloxy)-5-isopropoxy-N-(pyrazol-3-yl) benzamide,
3-(6-ethanesulphonylpyridin-3-yloxy)-5-isopropoxy-N-(1-methyl-1H-pyrazol-3-yl) benzamide,
3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(pyrazol-3-yl) benzamide,
3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(pyridin-2-yl) benzamide,
3-(6-ethanesulfonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide,
5-(2-fluoro-1-methyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,
5-(2-chloro-1-methyl-ethoxy)-3-(6-ethanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,
5-(2-fluoro-1-fluoromethyl-ethoxy)-N-(isoxazol-3-yl)-3-(6-methanesulphonylpyridin-3-yloxy) benzamide,
5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(pyridin-2-yl) benzamide,
5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(3-methyl-[1,2,4]-thiadiazol-5-yl) benzamide,
3-(4-dimethyl sulphamoyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(3-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-3-(6-isopropyl sulfonyl pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,
3-(3-chloro-4-methanesulphonylphenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(pyridin-3-yloxy) benzamide,
5-(2-fluoro-1-fluoromethyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(pyridin-3-yloxy) benzamide,
5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(pyridin-4-yloxy) benzamide,
5-(2-fluoro-1-fluoromethyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(pyridin-4-yloxy) benzamide,
2-[3-(6-ethanesulphonylpyridin-3-yloxy)-5-(1-methyl-1H-pyrazol-3-yl carbamoyl)-phenoxy] propionic acid,
5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(3-fluoro-4-methanesulphonylphenoxy)-N-(1-methyl-1H-

pyrazol-3-yl) benzamide or pharmacologically acceptable salts thereof.

(16) A compound which is 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl-phenoxy)-N-thiazol-2-yl-benzamide or pharmacologically acceptable salts thereof.

(17) A compound which is N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonyl-phenoxy)-5-(1-methoxymethyl-propoxy)-benzamide or pharmacologically acceptable salts thereof.

(18) A compound which is 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl-phenoxy)-N-pyridin-2-yl-benzamide or pharmacologically acceptable salts thereof.

(19) A compound which is 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl-phenoxy)-N-(2-methylthiazol-4-yl)-benzamide or pharmacologically acceptable salts thereof.

(20) A compound which is 5-(2-hydroxy-1-methyl-ethoxy)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide or pharmacologically acceptable salts thereof.

(21) A compound which is 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl-phenoxy)-N-(3-methyl-[1,2,4]-thiadiazol-5-yl)-benzamide or pharmacologically acceptable salts thereof.

(22) A compound which is 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl-phenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide or pharmacologically acceptable salts thereof.

(23) A compound which is 3-(3-fluoro-4-methanesulphonyl-phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide or pharmacologically acceptable salts thereof.

(24) A compound which is 3-(6-ethane sulfonyl-pyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide or pharmacologically acceptable salts thereof.

(25) A compound which is 3-(6-ethane sulfonyl-pyridin-3-yloxy)-5-isopropoxy-N-(1-methyl-1H-pyrazol-3-yl) benzamide or pharmacologically acceptable salts thereof.

(26) A compound which is 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonyl-pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide or pharmacologically acceptable salts thereof.

(27) A compound which is 3-(6-ethane sulfonyl-pyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl) benzamide or pharmacologically acceptable salts thereof.

(28) A compound which is 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonyl-pyridin-3-yloxy)-N-(pyrazol-3-yl) benzamide or pharmacologically acceptable salts thereof.

(29) A medicinal composition which is formed from the following (1) to (3) to be used for treatment prevention and/or delaying the development of type II diabetes.

(1). The compound which is represented by formula (I).
(2). One or more compounds selected from the group comprising following (a)-(g).
(a) Other glucokinase activator.
(b) Bisguanide.
(c) PPAR agonist.
(d) Insulin.
(e) Somatostatin.
(f) α-glucosidase inhibitor, and
(g) Insulin secretion promoter.
(3). Pharmacologically acceptable carriers.

(30) A glucokinase activator, wherein the effective ingredient comprises the compound in accordance with any of aforsaid (1) - (28).

(31) An agent for preventing and/or treating diabetes, wherein the effective ingredient comprises the compound in accordance with any of aforsaid (1) - (28).

(32) An agent for prevention and/or therapy of obesity, wherein the effective ingredient comprises the compound in accordance with any of aforsaid (1) - (28).

Meaning of term used in below this specification is described, and further it is described in greater detail about the compound in accordance with this invention.

As "aryl group", for example phenyl group, hydrocarbon ring aryl group and the like of carbon number 6-14 such as for example naphthyl group, biphenyl group, anthryl group and the like are nominated.

As "lower alkyl group", alkyl group having preferably 1-6 C straight chain or branched is meant, and for example methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group; isoamyl group, neopentyl group, isopentyl group, 1,1-dimethylpropyl group, 1-methylbutyl group, 2-methyl butyl group, 1,2-dimethylpropyl group, hexyl group, isohexyl group, 1-methyl pentyl group, 2-methyl pentyl group, 3-methyl pentyl group, 1,1-dimethylbutyl group, 1,2-dimethyl butyl group, 2,2-dimethylbutyl group, 1,3-dimethylbutyl group, 2,3-dimethyl butyl group, 3,3-dimethyl butyl group, 1-ethyl butyl group, 2-ethyl butyl group, 1,2,2-trimethylpropyl group, 1-ethyl-2-methylpropyl group and the like are nominated.

A "lower alkenyl group" refers to lower alkenyl group of branched chain form or straight chain form of 1-6 C, and for example vinyl group, allyl group, 1-butenyl group, 2-butenyl group, 1-pentenyl group and the like are nominated.

As "alkoxy group", the group which substituted hydrogen atom of hydroxy group with the aforesaid lower alkyl group is meant, and for example methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, sec-butoxy group, tert butoxy group, pentyloxy group, isopentyloxy group, hexyloxy group, isohexyloxy group and the like are nominated.

As 'heteroaryl group', the 5-7 membered monocycle which had 1-3 heteroatom which was selected from the group comprising-oxygen atom, sulfur atom and nitrogen atom was meant, or heteroaryl group of said monocycle and pyridine ring or benzene ring were condensed is meant, and for example furyl group, thienyl group, pyrrolyl group, imidazolyl group, triazolyl group, thiazolyl group, thiadiazolyl group, isothiazolyl group, oxazolyl group, isoxazolyl group, pyridyl group, pyrimidinyl group, pyridazinyl group, pyrazolyl group, pyrazinyl group, quinolyl group, isoquinolyl group, quinazolinyl group, quinolidinyl group, quinoxalinyl group, cinnolinyl group, benzimidazolyl group, imidazopyridyl group, benzofuranyl group, naphthyridinyl group, 1,2-benzo isoxazolyl group, benzoxazolyl group, benzothiazolyl group, oxazolo pyridyl group, pyrido thiazolyl group, isothiazolo pyridyl group, benzothienyl group and the like are nominated.

As "halogen atom", for example fluorine atom, chlorine atom, bromine atom and iodine atom are meant.

As "hydroxyalkyl group", one hydrogen atom in the said lower alkyl group means group substituted by hydroxy group, and for example hydroxymethyl group, hydroxyethyl group, 1-hydroxypropyl group, 1-hydroxyethyl group, 2-hydroxypropyl group, 2-hydroxy-1-methyl-ethyl group and the like are

nominated.

As "alkylcarbamoyl group", mono substituted carbamoyl group is meant with the aforesaid lower alkyl group, and for example methylcarbamoyl group, ethyl carbamoyl group, propyl carbamoyl group, isopropyl carbamoyl group, butyl carbamoyl group, sec-butyl carbamoyl group, tert-butyl carbamoyl group and the like are nominated.

As "dialkyl carbamoyl group", carbamoyl group disubstituted by same or different the aforesaid lower alkyl group is meant, and, as "dialkyl carbamoyl group", for example dimethylcarbamoyl group, diethylcarbamoyl group, ethylmethyl carbamoyl group, dipropyl carbamoyl group, methylpropyl carbamoyl group, diisopropyl carbamoyl group and the like are nominated.

As "alkylamino group", mono substituted amino group is meant by the aforesaid lower alkyl group, and for example methylamino group, ethylamino group-propylamino group-isopropyl-amino group, butyl amino group, sec-butylamino group or tert-butylamino group and the like are nominated.

As "dialkylamino group", amino group disubstituted by same or different the aforesaid lower alkyl group is meant, and for example dimethylamino group, diethylamino group, dipropylamino group, methylpropyl amino group or diisopropylamino group and the like are nominated.

As "amino alkyl group", 1 of hydrogen atom composing said alkyl group means group substituted by amino group, and for example aminomethyl group, amino ethyl group, aminopropyl group and the like are nominated.

As "alkanoyl group", said alkyl group and carbonyl group mean bonded group, and for example methyl carbonyl group, ethyl carbonyl group, propyl carbonyl group, isopropyl carbonyl group and the like are nominated.

As "alkanoyl amino group", said alkanoyl group and amino group mean bonded group, and for example methyl carbonylamino group, ethyl carbonylamino group, isopropyl carbonylamino group and the like are nominated.

As "alkanoyl amino alkyl group", one hydrogen atom of said alkyl group means group substituted by said alkanoyl amino group, and for example acetylamino methyl group, ethyl carbonylamino methyl group, methyl carbonylamino ethyl group, isopropyl carbonylamino methyl group and the like are

nominated.

As "alkylthio group", said alkyl group and sulfur atom mean bonded group, and for example methylthio group, ethylthio group, propylthio group, isopropylthio group and the like are nominated.

An "alkylsulfonyl group" means a group in which said alkyl group and sulphonyl group are bonded group, and for example methylsulfonyl group, ethylsulfonyl group, propyl sulphonyl group, isopropyl sulphonyl group and the like are nominated.

An "alkylsulfonyl amino group" means a group in which a hydrogen atom of amino group is mono substituted with said alkylsulfonyl group, and for example methylsulphonylamino group, ethylsulfonyl amino group, propyl sulfonyl amino group or isopropyl sulfonyl amino group and the like are nominated.

An "alkoxycarbonyl group", means a group in which hydrogen atom of carboxyl group is substituted with said alkyl group, and for example methoxycarbonyl group, ethoxycarbonyl group, propyl carbonyl group, isopropyl carbonyl group and the like are nominated.

An "alkoxycarbonylamino group" means a group in which one hydrogen atom of amino group is substituted by said alkoxycarbonyl group, and for example methoxycarbonylamino group, ethoxycarbonylamino group, propyl carbonylamino group, isopropyl carbonylamino group and the like are nominated.

An "alkoxycarbonylamino alkyl group" means a group in which one hydrogen atom of said alkyl group is substituted by said alkoxycarbonylamino group, and for example methoxycarbonylamino methyl group, ethoxycarbonylamino methyl group, isopropyl carbonylamino ethyl group and the like are nominated.

An "alkyl sulphamoyl group", means a group in which one hydrogen atom of NH_2 in sulphamoyl group is substituted by the aforesaid lower alkyl group, and for example, methyl sulphamoyl group, ethyl sulphamoyl group, isopropyl sulphamoyl group and the like are nominated.

A "dialkyl sulphamoyl group" means a group in which two hydrogen atoms of NH_2 in sulphamoyl group are substituted by the same or different aforesaid lower alkyl group, and for example dimethyl sulphamoyl group, diethyl sulphamoyl group, ethylmethyl sulphamoyl group, diisopropyl sulphamoyl

group and the like are nominated.

In order to disclose further detail about the compounds represented by the aforesaid formula (I) of this invention, the various symbols used in formula (I) are explained with examples.

formula (II)

(II)

denotes a 6-10 membered aryl group or 5-7 membered heteroaryl group, which may have 1 or 2 substituents represented by the aforesaid R1 in the ring,

As "6-10 membered aryl group" represented by A ring, for example phenyl group, naphthyl group are nominated, among these, phenyl group is preferred.

As "5-7 membered heteroaryl group" represented by A ring, "5-7 membered heteroaryl group" of among "heteroaryl group" of the said definition and one of having the same meaning are nominated, among these, heteroaryl group of a member of five or six is preferred.

As "5-7 membered heteroaryl group" represented by A ring, for example furyl group, thienyl group, pyrrolyl group, imidazolyl group, triazolyl group, pyrazolyl group, thiazolyl group, thiadiazolyl group, isothiazolyl group, oxazolyl group, isoxazolyl group, pyridyl group, pyrimidinyl group, pyridazinyl group, pyrazinyl group are preferred. Among these, triazolyl group, thiazolyl group, thiadiazolyl group, pyridyl group and pyrazinyl group are more preferred, and triazolyl group, thiadiazolyl group, pyridyl group, are especially preferred.

As A ring, thiadiazolyl group, phenyl group or pyridyl group are preferred, and phenyl group or pyridyl group are more preferred.

Moreover, A ring may have 1 or 2 substituents represented by R1 in said ring. Wherein, R1 denotes group selected from the group comprising alkylsulfonyl group, alkanoyl group, alkyl group, hydroxyalkyl group, hydroxy group, alkylcarbamoyl group, alkyl sulphamoyl group, dialkyl sulphamoyl group, alkylthio group, alkoxy group, dialkyl carbamoyl group, alkoxycarbonylamino group, halogen atom, cyano group, alkoxycarbonyl group, alkanoyl amino alkyl group, alkylsulfonyl

amino alkyl group, alkoxycarbonylamino alkyl group and trifluoromethyl group, and when there are 2 substituents on A ring, these substituents may be the same or different.

As R1, alkylsulfonyl group, alkanoyl group, hydroxyalkyl group, alkylcarbamoyl group, alkyl sulphamoyl group, dialkyl sulphamoyl group, dialkyl carbamoyl group, alkoxycarbonylamino group, halogen atom, alkanoyl amino alkyl group, alkylsulfonyl amino alkyl group or alkoxycarbonylamino alkyl group are preferred, and alkylsulfonyl group, alkanoyl group, hydroxyalkyl group, halogen atom, alkanoyl amino alkyl group, alkylsulfonyl amino alkyl group or alkoxycarbonylamino alkyl group are preferred furthermore, and alkylsulfonyl group, alkanoyl group, halogen atom or hydroxyalkyl group is preferred furthermore, and alkylsulfonyl group is particularly preferred.

When A ring has R1 in said ring, the position on A ring to which R1 is bonded is not restricted in particular and may be any position which can be bonded.

When A ring is phenyl group, the bonding position of R1 on phenyl group is preferably located in para position with respect to X1 and bond of said phenyl group.

X1 denotes O, S or NH, and among these, O or S is preferred, and O is more preferred.

Accordingly when X1 is O and A ring is phenyl group, then as the -X1-A ring-R1, for example 4-(1-hydroxyethyl)-phenoxy group, 4-(1-hydroxypropyl)-phenoxy group, 4-methanesulphonylphenoxy group, 4-methyl carbonyl-phenoxy group, 4-methylcarbamoyl-phenoxy group, 4-ethyl carbonyl-phenoxy group, 4-dimethylcarbamoyl-phenoxy group, 4-methyl carbonylamino methyl-pheoxy, 4-methanesulphonyl aminomethyl-phenoxy group, 4-methoxycarbonylamino methyl-phenoxy group, 2-fluoro-phenoxy group, 4-methoxycarbonyl-phenoxy group, 4-hydroxymethyl-phenoxy group, 4-methanesulphonyl-2-fluoro-phenoxy group, 4-cyano-phenoxy group, 4-methyl-phenyloxy group, 4-trifluoromethyl-phenyloxy group, 3-fluoro-4-methanesulphonylphenoxy group, 4-dimethyl sulphamoyl phenoxy group, 3-chloro-4-methanesulphonylphenoxy group, 3-methanesulphonylphenoxy group are nominated, among these, 4-(1-hydroxyethyl)-phenoxy group, 4-(1-hydroxypropyl)-phenoxy group, 4-methanesulphonylphenoxy group, 4-methyl carbonyl-phenoxy group, 4-methylcarbamoyl-phenoxy group, 4-ethyl carbonyl-phenoxy group, 4-dimethylcarbamoyl-phenoxy group, 4-methyl carbonylamino methyl-phenoxy group, 4-methanesulphonyl aminomethyl-phenoxy group, 4-methoxycarbonylamino methyl-phenoxy group, 4-hydroxymethyl-phenoxy group, 4-methanesulphonyl 2-fluoro-phenoxy group, 3-fluoro-4-methanesulphony, 4-dimethylsulfamoylphenoxy group, 3-chloro-4-methanesulphonylphenoxy group are nominated. Moreover, 4-(1-hydroxyethyl)-phenoxy group, 4-

(1-hydroxypropyl)-phenoxy group, 4-methanesulphonylphenoxy group, 4-methyl carbonyl-phenoxy group, 4-ethyl carbonyl-phenoxy group, 4-methyl carbonylamino methyl-phenoxy group, 4-methanesulphonyl aminomethyl-phenoxy group, 4-methoxycarbonylamino methyl-phenoxy group, 4-hydroxymethyl-phenoxy group, 3-fluoro-4-methanesulphonylphenoxy group, 4-dimethyl sulphamoyl phenoxy group, 3-chloro-4-methanesulphonylphenoxy group more preferred, and among these, 4-(1-hydroxyethyl)-phenoxy group, 4-(1-hydroxypropyl)-phenoxy group, 4-methanesulphonylphenoxy group, 4-methyl carbonyl-phenoxy group, 4-ethyl carbonyl-phenoxy group, 4-hydroxymethyl-phenoxy group, or 3-fluoro-4-methanesulphonylphenoxy group are preferred furthermore, and among these, 4-methanesulphonylphenoxy group is particularly preferred.

Moreover, when A ring is phenyl group and X1 is S, as –X1-A ring-R1 group, for example, 4-fluoro-phenyl sulphanyl group, 4-methyl-phenyl sulphanyl group, 4-trifluoromethyl-phenyl sulphanyl group, 4-(1-hydroxyethyl)-phenyl sulphanyl group, 4-methanesulphonyl phenyl sulphanyl group, 4-methyl carbonyl-phenyl sulphanyl group, 4-ethyl carbonyl-phenyl sulphanyl group, 4-methylcarbamoyl-phenyl sulphanyl group, 4-dimethylcarbamoyl-phenyl sulphanyl group, 4-methyl carbonylamino methyl-phenylsulfanyl group, 4-methylsulfonylaminomethyl-phenylsulfanyl group, 4-methoxycarbonyl-phenyl sulphanyl group, 4-methoxycarbonyl-aminomethyl-phenyl sulphanyl group, 4-hydroxymethyl-phenyl sulphanyl group, 4-cyano-phenyl sulphanyl group and the like. Among these, 4-fluoro-phenyl sulphanyl group, 4-(1-hydroxyethyl)-phenyl sulphanyl group, 4-methanesulphonyl phenyl sulphanyl group, 4-methyl carbonyl-phenyl sulphanyl group, 4-ethyl carbonyl-phenyl sulphanyl group, 4-methylcarbamoyl-phenyl sulphanyl group, 4-dimethylcarbamoylphenylsulfanyl group, 4-methylcarbonylaminomethyl-phenylsulfanyl group, 4-methylsulphonylamino methyl-phenyl sulphanyl group, 4-methoxycarbonyl-aminomethyl-phenyl sulphanyl group or 4-hydroxymethyl-phenyl sulphanyl group are preferred, and 4-(1-hydroxyethyl)-phenyl sulphanyl group, 4-methanesulphonyl phenyl sulphanyl group, 4-methyl carbonyl-phenyl sulphanyl group, 4-ethyl carbonyl-phenyl sulphanyl group, 4-methyl carbonylamino methyl-phenyl sulphanyl group, 4-methylsulphonylamino methyl-phenyl sulphanyl group, 4-methoxycarbonyl-aminomethyl-phenyl sulphanyl group or 4-hydroxymethyl-phenyl sulphanyl group more preferred, among these, 4-(1-hydroxyethyl)-phenyl sulphanyl group, 4-methanesulphonyl phenyl sulphanyl group, 4-methyl carbonyl-phenyl sulphanyl group, 4-ethyl carbonyl-phenyl sulphanyl group or 4-hydroxymethyl-phenyl sulphanyl group are preferred furthermore, among these, 4-methanesulphonyl phenyl sulphanyl group is particularly preferred.

When A ring is 5-7 membered heteroaryl group and X1 is S, then as -X1-A ring-R1, for example, 5-cyano-pyridin-2-yl sulphanyl group, 5-bromo-pyridin-2-yl sulphanyl group, 5-methoxycarbonyl-

pyridin-2-yl sulphanyl group, 5-hydroxymethyl-pyridin-2-yl sulphanyl group, 5-methanesulphonylpyridin-2-yl sulphanyl group, 5-methyl-pyridin-2-yl sulphanyl group, 5-trifluoromethyl-pyridin-2-yl sulphanyl group, pyridin-2-yl sulphanyl group, pyridin-4-yl sulphanyl group, 6-methyl-pyridin-3-yl sulphanyl group, [1,3,4]thiadiazol-2-yl sulphanyl group, 5-methylthio-[1,3,4] thiadiazol-2-yl sulphanyl group, 5-methanesulphonyl [1,3,4] thiadiazol-2-yl sulphanyl group, [1,2,4]-triazol-3-yl sulphanyl group, furan-3-ylsulfanyl group, thiophen-3-ylsulfanyl group, pyrrole-3-yl sulphanyl group, imidazol-2-yl sulphanyl group, thiazol-2-yl sulphanyl group, oxazol-2-yl sulphanyl group, isoxazol-3-yl sulphanyl group, pyrazin-2-yl sulphanyl group, pyrimidin-2-yl sulphanyl group, pyridazin-3-yl sulphanyl group, 3H-pyrazol-3-yl sulphanyl group and the like are nominated. Among these, 5-bromo-pyridin-2-yl sulphanyl group, 5-hydroxymethyl-pyridin-2-yl sulphanyl group, 5-methanesulphonylpyridin-2-yl sulphanyl group, pyridine-2 yl sulphanyl group, pyridin-4-yl sulphanyl group, [1,3,4] thiadiazol-2-yl sulphanyl group, 5-methanesulfonyl[1,3,4]thiadiazol-2-ylsulfanyl group, [1,2,4]-triazol-3-yl sulphanyl group, furan-3-yl sulphanyl group, thiophen-3-yl sulphanyl group, pyrrole-3-yl sulphanyl group, imidazol-2-yl sulphanyl group, thiazol-2-yl sulphanyl group, oxazol-2-yl sulphanyl group, isoxazol-3-yl sulphanyl group, pyrazin-2-yl sulphanyl group, pyrimidin-2-yl sulphanyl group, pyridazin-3-yl sulphanyl group, 3H-pyrazol-3-yl sulphanyl group are preferred. Among these, 5-hydroxymethyl-pyridin-2-yl sulphanyl group, 5-methanesulphonylpyridin-2-yl sulphanyl group, pyridine-2 yl sulphanyl group, pyridin-4-yl sulphanyl group, [1,3,4] thiadiazol-2-yl sulphanyl group, 5-methanesulphonyl [1,3,4] thiadiazol-2-yl sulphanyl group, [1,2,4]-triazol-3-yl sulphanyl group, thiazol-2-yl sulphanyl group or pyrazin-2-yl sulphanyl group more preferred, among these, 5-hydroxymethyl-pyridin-2-yl sulphanyl group, 5-methanesulphonylpyridin-2-yl sulphanyl group, pyridine-2 yl sulphanyl group, pyridin-4-yl sulphanyl group, [1,3,4] thiadiazol-2-yl sulphanyl group, 5-methanesulphonyl [1,3,4] thiadiazol-2-yl sulphanyl group, [1,2,4]-triazol-3-yl sulphanyl group or thiazol-2-yl sulphanyl group are preferred furthermore, and among these, pyridine-2 yl sulphanyl group, pyridin-4-yl sulphanyl group, [1,3,4] thiadiazol-2-yl sulphanyl group, [1,2,4]-triazol-3-yl sulphanyl group or thiazol-2-yl sulphanyl group are particularly preferred.

When A ring is 5-7 membered heteroaryl group, X1 is O, then as -X1-A-ring-R1, for example, pyrimidin-4-yloxy group, pyridazin-3-yloxy group, pyrazin-2-yloxy group, pyridin-2-yloxy group, 2-hydroxy-pyridin-3-yloxy group, 2-hydroxy-pyridin-4-yloxy group, 5-hydroxymethyl-pyridin-2-yloxy group, 5-methyl carbonyl-pyridin-2-yloxy group, 5-(1-hydroxyethyl)-pyridin-2-yloxy group, 5-methoxycarbonylamino methyl-pyridin-2-yloxy group, 5-methanesulphonylpyridin-2-yloxy group, 5-methoxycarbonyl-pyridin-2-yloxy group, 5-cyano-pyridin-2-yloxy group, 5-bromo-pyridin-2-yloxy group, 5-dimethylcarbamoyl-pyridin-2-yloxy group, 5-methoxycarbonyl-pyridin-2-yloxy group 5-methyl carbonylamino methyl-pyridin-2-yloxy group, 5-trifluoromethyl-pyridin-2-yloxy group, 5-

methyl carbonyl-imidazol-2-yloxy group, 6-hydroxymethyl-pyrimidin-2-yloxy group, 6-methyl carbonyl-pyrimidin-2-yloxy group, 6-methanesulfonylpyrimidin-2-yloxy group, 6-hydroxymethyl-pyrimidazin-3-yloxy group, 6-methyl carbonyl-pyridazin-3-yloxy group, 6-methanesulphonyl pyridazin-3-yloxy group, 5-hydroxymethyl-pyrazin-2-yloxy group, 5-methyl carbonyl-pyrazin-2-yloxy group, 5-methanesulphonyl pyrazin-2-yloxy group, 6-ethanesulphonyl pyridin-3-yloxy group, 6-methanesulfonylpyridin-3-yloxy group, pyridin-3-yloxy group, pyridin-4-yloxy group, 6-isopropyl sulfonyl pyridin-3-yloxy group and the like are nominated. Among these, pyrimidin-4-yloxy group, pyridazin-3-yloxy group, pyrazin-2-yloxy group, pyridin-2-yloxy group, 2-hydroxy-pyridin-3-yloxy group, 2-hydroxy-pyridin-4-yloxy group, 5-hydroxymethyl-pyridin-2-yloxy group, 5-methyl carbonyl-pyridin-2-yloxy group, 5-(1-hydroxyethyl)-pyridin-2-yloxy group, 5-methoxycarbonylamino methyl-pyridin-2-yloxy group, 5-methanesulphonylpyridin-2-yloxy group, 5-bromo-pyridin-2-yloxy group, 5-dimethylcarbamoyl-pyridin-2-yloxy group, 5-methyl carbonylaminomethylpyridin-2-yloxy group, 5-methyl carbonylaminomethylimidazl-2-yloxy group, 6-hydroxymethyl-pyrimidin-2-yloxy group, 6-methyl carbonyl-pyrimidin-2-yloxy group, 6-methanesulphonyl pyrimidin-2-yloxy group, 6-hydroxymethyl-pyridazin-3-yloxy group, 6-methyl carbonyl-pyridazin-3-yloxy group, 6-methanesulphonylpyridazin-3-yloxy group, 5-hydroxymethyl pyrazin-2-yloxy group, 5-methyl carbonyl-pyrazin-2-yloxy group, 5-methanesulphonyl pyrazin-2-yloxy group, 6-ethanesulfonylpyridin-3-yloxy group, 6-methanesulphonylpyridin-3-yloxy, pyridin-3-yloxy group, pyridin-4-yloxy group are preferred. Among these, pyrazin-2-yloxy group, pyridin-2-yloxy group, 2-hydroxy-pyridin-3-yloxy group, 2-hydroxy-pyridin-4-yloxy group, 5-hydroxymethyl-pyridin-2-yloxy group, 5-methyl carbonyl-pyridin-2-yloxy group, 5-(1-hydroxyethyl)-pyridin-2-yloxy group, 5-methoxycarbonylamino methyl-pyridin-2-yloxy group, 5-methanesulphonylpyridin-2-yloxy group, 5-methyl carbonylamino methyl-pyridin-2-yloxy group, 5-hydroxymethyl-pyrazin-2-yloxy group, 5-methyl carbonyl-pyrazin-2-yloxy group, 5-methanesulfonyl-pyrazin-2-yloxy group, 6-ethanesulphonylpyridin-3-yloxy group, 6-methanesulphonylpyridin-3-yloxy group are more preferred, and among these, 2-hydroxy-pyridin-3-yloxy group, 2-hydroxy-pyridin-4-yloxy group, 5-hydroxymethyl-pyridin-2-yloxy group, 5-methyl carbonyl-pyridin-2-yloxy group, 5-(1-hydroxyethyl)-pyridin-2-yloxy group or 5-methanesulphonylpyridin-2-yloxy group, 6-methanesulphonylpyridin-3-yloxy group, 6-ethanesulfonylpyridin-3-yloxy group are preferred furthermore.

X2 shows O, S or CH_2, among these, O or CH2 is preferred, and O is more preferred.

R2 may have 1 or 2 substituent groups selected from the group comprising halogen atom, carboxyl group, alkoxycarbonyl group, hydroxy group, amino group (further said amino group may be substituted with 1 or 2 alkanoyl group or lower alkyl group), alkoxy group and N-alkylcarbamoyl

group, and shows 3-7 C cyclic alkyl group, lower alkenyl group or lower alkyl group of branched or straight chain.

As " halogen atom" represented by R2, the same groups as aforesaid said definition are nominated. Among these, chlorine atom or fluorine atom is preferred.

An "alkoxycarbonyl group" represented by R2 menas a carbonyl group having alkoxy group of the said definition, and for example methoxycarbonyl group, ethoxycarbonyl group, propyl oxycarbonyl group, isopropyl oxycarbonyl group, tert-butyloxycarbonyl group and the like are nominated.

As "3-7 C cyclic alkyl group" represented by R2, for example cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group and the like are nominated, among these, cyclopentyl group or cyclohexyl group is preferred, and cyclopentyl group are more preferred.

When R2 composes 3-7 C cyclic alkyl group, 1 arbitrary carbon atom of the carbon atoms composing said ring except the carbon atom bonded to X2 may be replaced by oxygen atom, NH, N-alkanoyl group or CONH.

As "the group where 1 carbon atom composing 3-7 C cyclic alkyl group (except carbon atom bonded with X2) is substituted by oxygen atom, NH, N-alkanoyl group or CONH" represented by R2, the carbon atom is replaced by oxygen atom, NH or N-alkanoyl group, more preferably by oxygen atom or N-alkanoyl. In a further embodiment, R2 is preferably, for example, tetrahydrofuranyl group, tetrahydropyranyl group, pyrrolidinyl group, piperidinyl group, N-acetyl piperidinyl group and, as said R2, tetrahydrofuranyl group, tetrahydropyranyl group or N-acetyl piperidinyl group are more preferred.

As "lower alkyl group of branched or straight chain" represented by R2, lower alkyl group of the said definition and same meaning is denoted.

As said lower alkyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group are preferred, and propyl group, isopropyl group, isobutyl group, sec-butyl group are more preferred.

As the "lower alkenyl group" represented by R2, the one how the aforesaid definition and is same is nominated, among these, propenyl group, isopropenyl group, isobutenyl group are preferred, and isopropenyl group is more preferred.

As R2, it is preferably, 3-7C cyclic alkyl group, lower alkyl group of branched or straight chain, or the group of 3-7C cyclic alkyl group where 1 carbon atom (except carbon atom bonded with X2) of among carbon atom composing said ring) is replaced by oxygen atom, NH, N-alkanoyl group or CONH, preferably lower alkyl group of branched or straight chain, or the group of 3-7C cyclic alkyl group where 1 carbon atom (except carbon atom bonded with X2) of among carbon atom composing said ring) is replaced by oxygen atom, NH, N-alkanoyl group or CONH.

Accordingly, as -X2-R2, for example, propyl group, isobutyl group, sec-butyl group, 3-methoxy-2-methyl-propyl group, 2-methoxymethyl-butyl group, 4-hydroxy-2-methyl-butyl group, 2-hydroxymethyl-butyl group, 3-hydroxy-butyl group, 3-methoxy butyl group, 3-hydroxy-2-methyl-propyl group, 3-hydroxy-butyl group, 3-methylcarbamoyl-propyl group, 3-acetylamino-2-methyl-propyl group, 2-hydroxymethyl-3-propenyl group, 2-methyl-2-propenyl group, ethoxy group, isopropoxy group, 2-methoxy-1-methyl-ethoxy group, 1-methoxymethyl-propoxy group, 3-hydroxy-1-methyl-propoxy group, 1-hydroxymethyl-propoxy group, 2-amino-1-ethoxy group, 2-hydroxy-propoxy group, 2-methoxy propoxy group, 2-hydroxy-1-methyl-ethoxy group, 2-hydroxy-ethoxy group, 2-dimethylamino-1-methyl-ethoxy group, 1-carboxy-ethoxy group, 2-methylcarbamoyl-ethoxy group, 2-acetylamino-1-methyl-ethoxy group, cyclopentyl oxy group, cyclohexyl oxy group, cycloheptyl oxy group, 2-hydroxy-cyclopentyl oxy group, tetrahydrofuran-3-yloxy group, tetrahydrofuran-2-yloxy group, tetrahydrofuran-4-yloxy group, piperidine-4-yloxy group, piperidine-3-yloxy group, pyrrolidine-3-yloxy group, pyrrolidine-2-yloxy group, 1-acetyl-piperidine-4-yloxy group, 1-acetyl-piperidine-3-yloxy group, 3-allyloxy group, 3-isopropenyl oxy group, 1-methyl-allyloxy group, 2-fluoro-1-fluoromethyl-ethoxy group, 2-fluoro-1-methyl-ethoxy group, 2-chloro-1-methyl-ethoxy group and the like are nominated. Among these, ethoxy group, isopropoxy group, 2-methoxy-1-methyl-ethoxy group, 1-methoxymethyl-propoxy group, 3-hydroxy-1-methyl-propoxy group, 1-hydroxymethyl-propoxy group, 2-hydroxy-propoxy group, 2-methoxy propoxy group, 2-hydroxy-1-methyl-ethoxy group, 2-hydroxy-ethoxy group, 2-methylcarbamoyl-ethoxy group, 2-acetylamino-1-methyl-ethoxy group, cyclopentyl oxy group, cyclohexyl oxy group, 2-hydroxy-cyclopentyl oxy group, tetrahydrofuran-3-yloxy group, tetrahydrofuran-2-yloxy group, tetrahydropyran-3-yloxy group, tetrahydrofuran-4-yloxy group, piperidine-4-yloxy group, piperidine-3-yloxy group, pyrrolidine-3-yloxy group, pyrrolidine-2-yloxy group, 1-acetyl-piperidine-4-yloxy group, 1-acetyl-piperidine-3-yloxy group, 3-isopropenyl oxy group, 1-methyl-allyloxy group, butyl group, isobutyl group, s-butyl group, 3-methoxy-2-methyl-propyl group, 2-methoxymethyl-butyl group, 4-hydroxy-2-methyl-butyl group, 2-hydroxymethyl-butyl group, 3-hydroxy-butyl group, 3-methoxybutyl group, 3-hydroxy-2-methyl-propyl group, 3-hydroxy-butyl group, 3-methylcarbamoyl-propyl group, 3-acetylamino-2-

methyl-propyl group, 2-hydroxymethyl-3-propenyl group, 2-methyl-2-propenyl group, 2-fluoro-1-fluoromethylethoxy group, 2-fluoro-1-methyl-ethoxy group, 2-chloro-1-methyl-ethoxy group are preferred. Wherein 2-methoxy-1-methyl-ethoxy group, 1-methoxymethyl-propoxy group, 3-hydroxy-1-methyl-propoxy group, 1-hydroxymethyl-propoxy group, 2-hydroxy-propoxy group, 2-methoxy propoxy group, 2-hydroxy-1-methyl-ethoxy group, 2-hydroxy-ethoxy group, 2-methylcarbamoyl-ethoxy group, 2-acetylamino-1-methyl-ethoxy group, cyclopentyl oxy group, cyclohexyl oxy group, 2-hydroxy-cyclopentyl oxy group, tetrahydrofuran-3-yloxy group, tetrahydropyran-3-yloxy group, 1-acetyl-piperidine-4-yloxy group, 1-acetyl-piperidine-3-yloxy group, 3-isopropenyl oxy group, 3-methoxy-2-methyl-propyl group, 2-methoxymethyl-butyl group, 4-hydroxy-2-methyl-butyl group, 2-hydroxymethyl-butyl group, 3-hydroxy-butyl group, 3-methoxybutyl group, 3-hydroxy-2-methyl-propyl group, 3-hydroxy-butyl group, 3-methylcarbamoyl-propyl group, 3-acetylamino-2-methyl-propyl group, 2-hydroxymethyl-3-propenyl group, 2-methyl-2-propenyl group, 2-fluoro-1-fluoromethyl-ethoxy group, 2-fluoro-1-methyl-ethoxy group are preferred furthermore, and among these, 2-methoxy-1-methyl-ethoxy group, 1-methoxymethyl-propoxy group, 3-hydroxy-1-methyl-propoxy group, 1-hydroxymethyl-propoxy group, 2-hydroxy-1-methyl-ethoxy group, 2-acetylamino-1-methyl-ethoxy group, 2-hydroxy-cyclopentyl oxy group, tetrahydrofuran-3-yloxy group, 1-acetyl-piperidine-4-yloxy group, 3-methoxy-2-methyl-propyl group, 2-methoxymethyl-butyl group, 4-hydroxy-2-methyl-butyl group, 2-hydroxymethyl-butyl group, 3-hydroxy-2-methyl-propyl group, 3-acetylamino-2-methyl-propyl group, 2-hydroxymethyl-3-propenyl group, 2-fluoro-1-fluoromethyl-ethoxy group are in particular preferred.

B ring is group represented by the aforesaid formula (III)

B ring

(III)

and shows a monocyclic or bicyclic heteroaryl group, where the carbon atom of the B ring which is bonded to the nitrogen atom of the amide group of the said formula (I) forms C=N with the nitrogen atom in said ring.

Wherein, the "heteroaryl group" represented by the B ring menas a "heteroaryl group" of the said definition represented by formula (III), where the carbon atom of the B ring bonded to the nitrogen atom in the amide bond represented by the aforesaid formula (I) forms C=N together with the nitrogen atom. Moreover, the double bond of C=N in B ring shown in the formula is a representation, and theB ring can be any as long as it is a heteroaryl group.

As B ring, the cases in which 5-alkoxycarbonyl-pyridin-2-yl group or 5-carboxyl-pyridin-2-yl group is not included in the heteroaryl group of said ring, are preferred, and the preferred cases are where a monocyclic or bicyclic heteroaryl group containing at least one heteroatom other than the nitrogen forming the C=N by bonding to the carbon which is bonded to the nitrogen of the amide group of the above-mentioned formula (I), wherein the heteroatom is selected from the group comprising nitrogen atom, sulfur atom and oxygen atom.

Moreover, especially preferred is a monocyclic or bicyclic heteroaryl group which contains at least one heteroatom selected from the group consisting of oxygen atom, sulfur atom and nitrogen atom (other than the nitrogen forming the C=N by bonding to the carbon which is bonded to the nitrogen of the amide group of the above-mentioned formula (I)) and when the B ring is thiazolyl group, said thiazole group 5-position substituent does not include isopropyl group

When B ring is monocycle, the number of atoms composing said monocycle is preferably 5 or 6, and it is more preferred to be 5.

Moreover, when B ring is a bicyclic ring, preferably it is of 9-10 members where a 5 or 6 membered monocycle is condensed with a benzene ring or pyridine ring, and 9-membered bicyclic ring of a 5 membered monocycle condensed with a pyridine ring is more preferred.

As B ring, in an embodiment, for example, thiazolyl group, imidazolyl group, isothiazolyl group, thiadiazolyl group, triazolyl group, oxazolyl group, isoxazolyl group, pyrazinyl group, pyridyl group, pyridazinyl group, pyrazolyl group, pyrimidinyl group, pyridothiazolyl group or benzothiazolyl group and the like are nominated, among these, thiazolyl group, thiadiazolyl group, isoxazolyl group, pyrazinyl group, pyridyl group, pyridothiazolyl group or pyrazolyl group are preferred, and thiazolyl group, thiadiazolyl group, isoxazolyl group, pyridothiazolyl group or pyrazolyl group are more preferred.

The B ring may have 1 or 2 substituents represented by R3 in said ring. Wherein, R3 denotes the group which are selected from the lower alkyl group, alkoxy group, alkylamino group, lower dialkylamino group, halogen atom, trifluoromethyl group, hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be substituted by lower alkyl group), amino alkyl group, alkanoyl group, carboxyl group, alkoxycarbonyl group and cyano group.

When B ring has 2 of the aforesaid R3 in ring, these may be being the same or different.

The bonding position of R3 on B ring is not limited in particular in either cases of B ring comprising of 5-7 membered monocyclic heteroaryl group or 9-11 membered bicyclic heteroaryl group, as long as it is the positions that can be bonded.

As R3, for example, among these, lower alkyl group, alkoxy group, halogen atom, hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be substituted by lower alkyl group), amino alkyl group or alkanoyl group are preferred, and lower alkyl group, hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be substituted by lower alkyl group), alkanoyl group are more preferred.

As R3, in an embodiment, for example methyl group, ethyl group, propyl group, isopropyl group, butyl group, methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, chlorine atom, fluorine atom, bromine atom, hydroxymethyl group, hydroxyethyl group, methoxy methyl group, ethoxyethyl group, methoxyethyl group, methoxycarbonyl group, ethoxycarbonyl group, propoxy carbonyl group, aminomethyl group, amino ethyl group, aminopropyl group, methyl carbonyl group, ethyl carbonyl group, propyl carbonyl group and the like are nominated. Among these, methyl group, ethyl group, chlorine atom, fluorine atom, hydroxymethyl group, hydroxyethyl group, methoxy methyl group, methoxyethyl group, methoxycarbonyl group, ethoxycarbonyl group, aminomethyl group, amino ethyl group, methyl carbonyl group, ethyl carbonyl group and the like are preferred, and methyl group, hydroxymethyl group, methoxy methyl group, methyl carbonyl group are more preferred.

Accordingly, as group represented by following formula (VII)

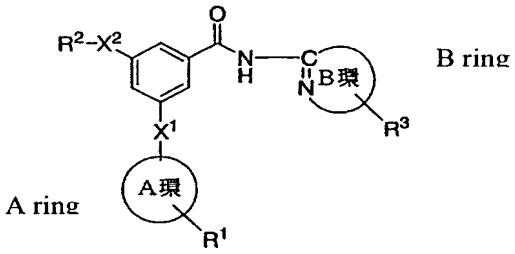
B ring

(VII)

(wherein, each symbol has the same the aforesaid definition) in an embodiment, for example it is preferably thiazol-2-yl group, 4-methyl-thiazol-2-yl group, 4-hydroxymethyl-thiazol-2-yl group, 4-methoxycarbonyl-thiazol-2-yl group, 4-methoxymethyl-thiazol-2-yl group, 4-aminomethyl-thiazol-2-yl group, 4-cyano-thiazol-2-yl group, 4-cyano-thiazol-2-yl group, 4-fluoro-thiazol-2-yl group, imidazol-2-yl group, 4-methyl-imidazol-2-yl group, 4-methoxycarbonyl-imidazol-2-yl group, isothiazol-3-yl group, 4-hydroxymethyl-iso thiazol-3-yl group, [1,3,4] thiadiazol-2-yl group, 5-acetyl-[1,3,41 thiadiazol-2-yl group, [1,2,4] triazol-2-yl group, 5-hydroxymethyl-[1,2,4] triazol-3-yl group, pyrazin-2-

yl group, pyridin-2-yl group, 4-methyl-pyridin-2-yl group, 4-methoxymethyl-imidazol-2-yl group, 4-acetyl-imidazol-2-yl group, 5-hydroxymethyl-imidazol-2-yl group, 5-methyl-[1,3,4] thiadiazol-2-yl group, 5-fluoro-[1,3,4] thiadiazol-2-yl group, 5-methyl-[1,2,4] triazol-2-yl group, 5-acetyl-[1,2,4] triazol-3-yl group, isoxazol-3-yl group, 4-methoxymethyl isoxazol-2-yl group, 5-methyl isoxazol-3-yl group, 5-hydroxymethyl-isoxazol-3-yl group, 5-methoxymethyl-isoxazol-3-yl group, 5-methyl carbonyl-isoxazol-3-yl group, 5-chloro-isoxazol-3-yl group, 5-aminomethyl-isoxazol-3-yl group, pyrazol-3-yl group, 4 methyl-1H-pyrazole-3-yl group, 6-methyl-pyridazin-3-yl group, thiazol-4-yl, 2-methyl-thiazol-4-yl, isoxazol-3-yl, thiazolo [5,4-b] pyridin-2-yl, 3-methyl-[1,2,4] thiadiazolyl-5-yl group, 1-methyl-1H-pyrazol-3-yl group.

In accordance with the above, the compound represented by Formula (I) in accordance with this invention,



(I)

(wherein each symbol has the same the aforesaid definition), as a further embodiment is for example 5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-(4-methylthiazol-2-yl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-ethoxy-3-(4-methanesulphonylphenoxy)-N-(4-methoxymethyl-thiazol-2-yl) benzamide, 5-cyclopentyloxy-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yloxy)-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methoxymethyl-ethoxy)-N-thiazol-2-yl-benzamide, 3-(2-fluoro-4-methanesulphonylphenoxy)-5-isopropoxy-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, 5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-pyrazol-3-yl-benzamide, 5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-pyrazin-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(3-methoxy-1-methyl-propoxy)-N-thiazol-2-yl-benzamide, 5-(3-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-pyrimidin-4-yl-benzamide, 5-isopropoxy-3-(4-

methanesulphonylphenoxy)-N-(pyrimidin-2-yl)-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzamide, N-(isoxazol-3-yl)-3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-benzamide, 3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-N-[1,3,4] thiadiazol-2-yl-benzamide, 5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-benzamide, 5-(2-amino-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(2-dimethylamino-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-propoxy)-3-(4-methanesulphonylphenoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, 3-(4-methanesulphonylphenoxy)-5-(2-methoxy-propoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, 5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-(thiazolo [5,4-b] pyridin-2-yl)-benzamide, 5-(2-hydroxymethyl-allyl)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazolo [5,4-b] pyridin-2-yl-benzamide, 5-(3-hydroxy-2-methyl-propyl)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-N-(4-methyl-thiazol-2-yl)-5-(piperidin-4-yl-oxy)-benzamide hydrochloride, 5-(1-acetyl-piperidine-4-yloxy)-3-(4-methanesulphonylphenoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, 2-[3-(4-methanesulphonylphenoxy)-5-(4-methyl-thiazol-2-yl-carbamoyl)-phenoxy] propionic acid, 5-(3-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(1-methylcarbamoyl-ethoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, 5-(2-acetylamino-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-pyridin-2-yl-benzamide, 5-(2-hydroxy-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-cyclopentyl oxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, N-(4-acetyl-thiazol-2-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-benzamide, 3-(3-fluoro-4-methanesulphonylphenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(5-methyl-thiazol-2-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-([1,2,4] thiadiazol-5-yl)-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(5-methoxycarbonyl-pyridin-2-yl)-benzamide, 6-[5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzoylamino] nicotinic acid, 5-(2-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-

N-(isoxazol-3-yl)-3-(4-methanesulphonylphenoxy)-benzamide, N-(5-hydroxymethyl-thiazol-2-yl)-5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(2-methylthiazol-4-yl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(4-methoxymethyl-thiazol-2-yl)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulfonylphenoxy)-N-(2-methylthiazol-4-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulfonylphenoxy)-N-(4-methoxymethylthiazol-4-yl) benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methylethoxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide, N-(2,5-dimethylthiazol-4-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-benzamide, 5-isopropoxy-3-(4-methoxycarbonylamino methylphenoxy)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(4-methylcarbamoyl-phenoxy)-N-thiazol-2-yl-benzamide, 3-(4-dimethylcarbamoyl-phenoxy)-5-isopropoxy-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(4-methyl carbonylamino methyl-phenoxy)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(4-methanesulphonyl aminomethyl-phenoxy)-N-thiazol-2-yl-benzamide, 3-[4-(1-hydroxy-propyl)-phenoxy]-5-isopropoxy-N-thiazol-2-yl-benzamide, 6-[3-isopropoxy-5-(thiazol-2-yl carbamoyl)-phenoxy]-nicotinic acid methyl ester, 3-(5-hydroxymethyl-pyridin-2-yl-oxy)-5-isopropoxy-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(5-methanesulphonylpyridin-2-yl)-N-thiazol-2-yl-benzamide, 3-(5-acetyl-pyridin-2-yl-oxy)-5-isopropoxy-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(5-methoxycarbonyl-pyrazin-2-yl-oxy)-N-thiazol-2-yl-benzamide, 3-(5-cyano-pyridin-2-yl-oxy)-5-isopropoxy-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(2-oxo-1,2-dihydro-pyridin-4-yl-oxy)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(2-oxo-1,2-dihydro-pyridin-3-yl-oxy)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(2-oxo-1,2-dihydro-pyridin-3-yl-oxy)-N-thiazolo[5,4-b]pyridin-2-yl-benzamide, 5-isopropoxy-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazolo [5,4-b]-pyridine-2-yl-benzamide, 5-isopropoxy-3-(4-methyl-[1,2,4] triazol-3-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-thiazol-2-yl sulphanyl-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(4H-[1,2,4] triazol-3-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(5-methyl sulphanyl-[1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(5-methyl-[1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-(tetrahydrofuran-3-yl-oxy)-N-thiazol-2-yl-3-(4H-[1,2,4] triazol-3-yl sulphanyl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(4-methyl-

thiazol-2-yl)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-benzamide, 5-(3-hydroxy-1-methyl-propoxy)-N-(4-methyl-thiazol-2-yl)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenyl sulphanyl)-N-thiazol-2-yl-benzamide, 3-(3-fluoro-phenylthio)-5-(2-hydroxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(pyridin-4-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methyl-pyridin-3-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(3-methyl-[1,2,4]-thiadiazol-5-yl)-benzamide, N-[3-hydroxymethyl-1,2,4-thiadiazol-5-yl]-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy) benzamide, 5-(3-hydroxy-1-methyl ethoxy)-3-(4-methanesulphonylphenoxy)-N-[5-methyl-1,2,4-thiadiazol-3-yl] benzamide, 5-(hydroxy-1-methyl ethoxy)-3-(4-methanesulphonylphenoxy)-N-(3-methoxy-1,2,4-thiadiazol-5-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(1,2,5-thiadiazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(4-trifluoromethyl-thiazol-2-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(4,5,6,7-tetrahydrobenzothiazol-2-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(pyridazin-3-yl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(3-isopropyl-[1,2,4]-triazol-5-yl)-3-(4-methanesulphonylphenoxy) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(3-methyl-[1,2,4]-oxadiazol-5-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-[4-(1-hydroxy-1-methyl-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy) benzamide, N-(4-cyano-thiazol-2-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(pyridin-2-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(5-methyl-isothiazol-3-yl) benzamide, 5-(3-hydroxy-cyclopentyl oxy)-3-(4-methanesulphonylphenoxy)-N-(thiazol-2-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(5-methoxy-thiazol-2-yl) benzamide, 5-(1-hydroxymethyl-2-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(thiazol-2-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(1H-[1,2,3] triazol-4-yl) benzamide, N-(1-acetyl-1H-pyrazol-3-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(pyrazol-3-yl) benzamide, N-(5,6-dihydro-4H-cyclopenta thiazol-2-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy) benzamide, 5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(thieno [3,2-d] thiazol-2-yl) benzamide, 3-(3-fluoro-4-methanesulphonylphenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-

ethoxy)-N-(pyrazol-3-yl) benzamide, 3-(4-cyano-phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(4-ethylsulfonyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(3-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(4-ethanesulphonyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-isopropyl sulfonyl phenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(4-hydroxy-4-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta thiazol-2-yl)-3-(4-methanesulphonylphenoxy) benzamide, 3-(4-dimethylcarbamoyl-phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(4-acetyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(1,3,4-thiadiazol-2-yl sulphanyl) benzamide, N-(1-ethyl-1H-pyrazol-3-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methoxycarbonylamino methyl-phenoxy)-N-(3-methyl-1,2,4-thiadiazol-5-yl) benzamide, 5-(1-hydroxymethyl-propoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-methanesulphonylpyridin-3-yloxy)-5-(1-methoxymethyl-propoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-isopropoxy-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenyl sulphanyl)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-cyclopropyl oxy-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-methanesulphonylpyridin-3-yloxy)-5-(1-methoxymethyl-propoxy)-N-(pyrazol-3-yl) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(1-hydroxymethyl-propoxy)-N-(1-methyl-1H-pyrazolyl-3-yl) benzamide, 5-(6-ethanesulfonylpyridin-3-yloxy)-3-(2-methoxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 2-[3-(4-methanesulphonylphenoxy)-5-(1-methyl-1H-pyrazol-3-yl carbamoyl)-phenoxy]propionic acid-tert-butyl ester, 3-(6-ethanesulfonylpyridin-3-yloxy)-5-(2-methoxy-1-methyl-ethoxy)-N-(pyrazol-3-yl)-benzamide, 3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl)-5-(tetrahydrofuran-3-yl) benzamide, N-(1-ethyl-1H-pyrazol-3-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(pyrazol-3-yl) benzamide, 3-(6-methanesulphonylpyridin-3-yloxy)-5-(2-methoxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-fluoro-1-fluoromethyl-ethoxy)-N-(1-methyl-

1H-pyrazol-3-yl) benzamide, 2-[3-(4-methanesulphonylphenoxy)-5-(1-methyl-1H-pyrazol-3-yl carbamoyl)-phenoxy]propionic acid, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-isopropoxy-N-(pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-isopropoxy-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(pyridin-2-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide, 5-(2-fluoro-1-methyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-chloro-1-methyl-ethoxy)-3-(6-ethanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-N-(isoxazol-3-yl)-3-(6-methanesulphonylpyridin-3-yloxy) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(pyridin-2-yl) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(3-methyl-[1,2,4]-thiadiazol-5-yl) benzamide, 3-(4-dimethyl sulphamoyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(3-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(6-isopropyl sulfonyl pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(3-chloro-4-methanesulphonylphenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(pyridin-3-yloxy) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(pyridin-3-yloxy) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(pyridin-4-yloxy) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(pyridin-4-yloxy) benzamide, 2-[3-(6-ethanesulphonylpyridin-3-yloxy)-5-(1-methyl-1H-pyrazol-3-yl carbamoyl)-phenoxy] propionic acid, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(3-fluoro-4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide and the like are nominated. Aamong these, for example 5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-(4-methylthiazol-2-yl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-ethoxy-3-(4-methanesulphonylphenoxy)-N-(4-methoxymethyl-thiazol-2-yl) benzamide, 5-cyclopentyloxy-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yloxy)-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methoxymethyl-ethoxy)-N-thiazol-2-yl-benzamide, 3-(2-fluoro-4-methanesulphonylphenoxy)-5-isopropoxy-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, 3-(4-methanesulphonylphenoxy)-5-(3-methoxy-1-methyl-propoxy)-N-thiazol-2-yl-benzamide, 5-(3-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzamide, N-(isoxazol-

3-yl)-3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-benzamide, 3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-N-[1,3,4] thiadiazol-2-yl-benzamide, 5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-benzamide, 5-(2-amino-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-propoxy)-3-(4-methanesulphonylphenoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, 3-(4-methanesulphonylphenoxy)-5-(2-methoxy-propoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, 5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-(thiazolo [5,4-b] pyridin-2-yl)-benzamide, 5-(2-hydroxymethyl-allyl)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazolo [5,4-b] pyridin-2-yl-benzamide, 5-(3-hydroxy-2-methyl-propyl)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(1-acetyl-piperidine-4-yloxy)-3-(4-methanesulphonylphenoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, 2-[3-(4-methanesulphonylphenoxy)-5-(4-methyl-thiazol-2-yl-carbamoyl)-phenoxy] propionic acid, 5-(3-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(2-acetylamino-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-pyridin-2-yl-benzamide, 5-(2-hydroxy-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-cyclopentyloxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, N-(4-acetyl-thiazol-2-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-benzamide, 3-(3-fluoro-4-methanesulphonylphenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(5-methyl-thiazol-2-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-([1,2,4] thiadiazol-5-yl)-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(5-methoxycarbonyl-pyridin-2-yl)-benzamide, 6-[5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzoylamino]nicotinic acid, 5-(2-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl)-3-(4-methanesulphonylphenoxy)-benzamide, N-(5-hydroxymethyl-thiazol-2-yl)-5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(2-methylthiazol-4-yl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-

(4-methoxymethyl-thiazol-2-yl)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide, N-(2,5-dimethylthiazol-4-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-benzamide, 5-isopropoxy-3-(4-methoxycarbonylamino methylphenoxy)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(4-methylcarbamoyl-phenoxy)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(4-methyl carbonylamino methyl-phenoxy)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(4-methanesulphonyl aminomethyl-phenoxy)-N-thiazol-2-yl-benzamide, 3-[4-(1-hydroxy-propyl)-phenoxy]-5-isopropoxy-N-thiazol-2-yl-benzamide, 6-[3-isopropoxy-5-(thiazol-2-yl carbamoyl)-phenoxy]-nicotinic acid methyl ester, 3-(5-hydroxymethyl-pyridin-2-yl-oxy)-5-isopropoxy-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(5-methanesulphonylpyridin-2-yl)-N-thiazol-2-yl-benzamide, 3-(5-acetyl-pyridin-2-yl-oxy)-5-isopropoxy-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(5-methoxycarbonyl-pyrazin-2-yl-oxy)-N-thiazol-2-yl-benzamide, 3-(5-cyano-pyridin-2-yl-oxy)-5-isopropoxy-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(2-oxo-1,2-dihydro-pyridin-4-yl-oxy)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(2-oxo-1,2-dihydro-pyridin-3-yl-oxy)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(2-oxo-1,2-dihydro-pyridin-3-yl-oxy)-N-thiazolo[5,4-b]pyridin-2-yl-benzamide, 5-isopropoxy-3-([1,3,4]thiadiazol-2-ylsulphanyl)-N-thiazolo[5,4-b]-pyridine-2-yl-benzamide, 5-isopropoxy-3-(4-methyl-[1,2,4]triazol-3-ylsulphanyl)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-thiazol-2-yl sulphanyl-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(4H-[1,2,4]triazol-3-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(5-methyl sulphanyl-[1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(5-methyl-[1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-(tetrahydrofuran-3-yl-oxy)-N-thiazol-2-yl-3-(4H-[1,2,4] triazol-3-yl sulphanyl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(4-methyl-thiazol-2-yl)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-benzamide, 5-(3-hydroxy-1-methyl-propoxy)-N-(4-methyl-thiazol-2-yl)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenyl sulphanyl)-N-thiazol-2-yl-benzamide, 3-(3-fluoro-phenylthio)-5-(2-hydroxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(pyridin-4-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methyl-pyridin-3-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(3-methyl-[1,2,4]thiadiazol-5-yl)-benzamide, N-[3-hydroxymethyl-1,2,4-thiadiazol-5-yl]-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy) benzamide, 5-(hydroxy-1-methyl ethoxy)-3-(4-methanesulphonylphenoxy)-N-(3-methoxy-1,2,4-thiadiazol-5-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-

(1,2,5-thiadiazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(3-isopropyl-[1,2,4]-triazol-5-yl)-3-(4-methanesulphonylphenoxy) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-[4-(1-hydroxy-1-methyl-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy) benzamide, N-(4-cyano-thiazol-2-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(pyridin-2-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(5-methyl-isothiazol-3-yl) benzamide, 5-(3-hydroxy-cyclopentyl oxy)-3-(4-methanesulphonylphenoxy)-N-(thiazol-2-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(5-methoxy-thiazol-2-yl) benzamide, 5-(1-hydroxymethyl-2-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(thiazol-2-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(1H-[1,2,3] triazol-4-yl) benzamide, N-(1-acetyl-1H-pyrazol-3-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(pyrazol-3-yl) benzamide, N-(5,6-dihydro-4H-cyclopenta thiazol-2-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy) benzamide, 5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(thieno[3,2-d]thiazol-2-yl) benzamide, 3-(3-fluoro-4-methanesulphonylphenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-N-(pyrazol-3-yl) benzamide, 3-(4-cyano-phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(4-ethylsulfonyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(3-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(4-ethanesulphonyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-isopropyl sulfonyl phenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(4-hydroxy-4-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta thiazol-2-yl)-3-(4-methanesulphonylphenoxy) benzamide, 3-(4-acetyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, N-(1-ethyl-1H-pyrazol-3-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methoxycarbonylamino methyl-phenoxy)-N-(3-methyl-1,2,4-thiadiazol-5-yl) benzamide, 5-(1-hydroxymethyl-propoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-methanesulphonylpyridin-3-yloxy)-5-(1-methoxymethyl-propoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-isopropoxy-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-

methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl) benzamide, 3-(6-methanesulphonylpyridin-3-yloxy)-5-(1-methoxymethyl-propoxy)-N-(pyrazol-3-yl) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(1-hydroxymethyl-propoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(6-ethanesulfonylpyridin-3-yloxy)-3-(2-methoxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-methoxy-1-methyl-ethoxy)-N-(pyrazol-3-yl)-benzamide, 3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl)-5-(tetrahydrofuran-3-yl) benzamide, N-(1-ethyl-1H-pyrazol-3-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(pyrazol-3-yl) benzamide, 3-(6-methanesulphonylpyridin-3-yloxy)-5-(2-methoxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-fluoro-1-fluoromethyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-isopropoxy-N-(pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-isopropoxy-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(pyridin-2-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide, 5-(2-fluoro-1-methyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-chloro-1-methyl-ethoxy)-3-(6-ethanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-N-(isoxazol-3-yl)-3-(6-methanesulphonylpyridin-3-yloxy) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(pyridin-2-yl) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(3-methyl-[1,2,4]-thiadiazol-5-yl) benzamide, 3-(4-dimethyl sulphamoyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(3-chloro-4-methanesulphonylphenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(pyridin-3-yloxy) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(pyridin-3-yloxy) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(pyridin-4-yloxy) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(pyridin-4-yloxy) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(3-fluoro-4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide and the like are preferred. Among these, for example, 5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-(4-methylthiazol-2-yl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yloxy)-N-thiazol-2-yl-benzamide, 3-(4-

methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methoxymethyl-ethoxy)-N-thiazol-2-yl-benzamide, 3-(2-fluoro-4-methanesulphonylphenoxy)-5-isopropoxy-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, 3-(4-methanesulphonylphenoxy)-5-(3-methoxy-1-methyl-propoxy)-N-thiazol-2-yl-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzamide, N-(isoxazol-3-yl)-3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-benzamide, 3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-N-[1,3,4] thiadiazol-2-yl-benzamide, 5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-benzamide, 5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-(thiazolo [5,4-b] pyridin-2-yl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazolo [5,4-b] pyridin-2-yl-benzamide, 5-(3-hydroxy-2-methyl-propyl)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(3-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(2-acetylamino-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-pyridin-2-yl-benzamide, 5-(2-hydroxy-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-cyclopentyl oxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, N-(4-acetyl-thiazol-2-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-benzamide, 3-(3-fluoro-4-methanesulphonylphenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-([1,2,4] thiadiazol-5-yl)-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide, 6-[5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzoylamino] nicotinic acid, 5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl)-3-(4-methanesulphonylphenoxy)-benzamide, N-(5-hydroxymethyl-thiazol-2-yl)-5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(2-methylthiazol-4-yl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(4-methoxymethyl-thiazol-2-yl)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-

3-yl-oxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide, N-(2,5-dimethyl thiazol-4-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-benzamide, 3-(5-acetyl-pyridin-2-yl-oxy)-5-isopropoxy-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(2-oxo-1,2-dihydro-pyridin-4-yl-oxy)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(2-oxo-1,2-dihydro-pyridin-3-yl-oxy)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(2-oxo-1,2-dihydro-pyridin-3-yl-oxy)-N-thiazolo [5,4-b] pyridin-2-yl-benzamide, 5-isopropoxy-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazolo [5,4-b]-pyridine-2-yl-benzamide, 5-isopropoxy-3-thiazol-2-yl sulphanyl-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(5-methyl-[1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(4-methyl-thiazol-2-yl)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-benzamide, 5-(3-hydroxy-1-methyl-propoxy)-N-(4-methyl-thiazol-2-yl)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenyl sulphanyl)-N-thiazol-2-yl-benzamide, 3-(3-fluoro-phenylthio)-5-(2-hydroxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(pyridin-4-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methyl-pyridin-3-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(3-methyl-[1,2,4]-thiadiazol-5-yl)-benzamide, 5-(hydroxy-1-methylethoxy)-3-(4-methanesulphonylphenoxy)-N-(3-methoxy-1,2,4-thiadiazol-5-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(3-isopropyl [1,2,4]-triazol-5-yl)-3-(4-methanesulphonylphenoxy) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-[4-(1-hydroxy-1-methyl-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(pyridin-2-yl) benzamide, 5-(1-hydroxymethyl-2-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(thiazol-2-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(pyrazol-3-yl) benzamide, N-(5,6-dihydro-4H-cyclopenta thiazol-2-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy) benzamide, 5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(3-fluoro-4-methanesulphonylphenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-N-(pyrazol-3-yl) benzamide, 3-(4-ethylsulfonyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(4-ethanesulphonyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-isopropyl sulfonyl phenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(4-hydroxy-4-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta thiazol-2-yl)-3-(4-methanesulphonylphenoxy) benzamide, 3-(4-acetyl phenoxy)-5-(2-

hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methoxycarbonylamino methyl-phenoxy)-N-(3-methyl-1,2,4-thiadiazol-5-yl) benzamide, 5-(1-hydroxymethyl-propoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-methanesulphonylpyridin-3-yloxy)-5-(1-methoxymethyl-propoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-isopropoxy-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl) benzamide, 3-(6-methanesulphonylpyridin-3-yloxy)-5-(1-methoxymethyl-propoxy)-N-(pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(1-hydroxymethyl-propoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(6-ethanesulphonylpyridin-3-yloxy)-3-(2-methoxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, a3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-methoxy-1-methyl-ethoxy)-N-(pyrazol-3-yl)-benzamide, N-(1-ethyl-1H-pyrazol-3-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(pyrazol-3-yl) benzamide, 3-(6-methanesulphonylpyridin-3-yloxy)-5-(2-methoxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-isopropoxy-N-(pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-isopropoxy-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide 5-(2-fluoro-1-methyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(3-methyl-[1,2,4]-thiadiazol-5-yl) benzamide, 3-(4-dimethyl sulphamoyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(3-chloro-4-methanesulphonylphenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide and the like are more preferred, and moreover for example, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yloxy)-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzamide, N-(isoxazol-3-yl)-3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-benzamide, 3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-N-[1,3,4] thiadiazol-2-yl-benzamide, 5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-

propoxy)-benzamide, 5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-(thiazolo [5,4-b] pyridin-2-yl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazolo [5,4-b]-pyridin-2-yl-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-pyridin-2-yl-benzamide, 5-(2-hydroxy-cyclopentyloxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-([1,2,4] thiadiazol-5-yl)-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(2-methylthiazol-4-yl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(4-methoxymethyl-thiazol-2-yl)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide, N-(2,5-dimethyl thiazol-4-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-benzamide, 5-isopropoxy-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazolo [5,4-b]-pyridine-2 yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(3-methyl-[1,2,4]-thiadiazol-5-yl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(3-fluoro-4-methanesulphonylphenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl) benzamide, the compound which is 5-(2-fluoro-1-fluoromethyl one ethoxy)-3-(6-methanesulphonylpyridin-3-yloxy)-N-(pyrazol-3-yl) benzamide, 3-(6-ethanesulphonylpyridin-3-yloxy)-5-isopropoxy-N-(1-methyl-1H-pyrazol-3-yl) benzamide and the like are particularly preferred.

Moreover, the heteroaryl carbamoyl benzene derivatives in accordance with this invention can exist as pharmacologically acceptable salt. As the aforesaid salt, acid addition salt or base addition salt is nominated.

As for the compound in accordance with this invention, there are case that stereoisomers such as optical isomers, diastereoisomers, geometric isomers or the like or tautomer are present due to the forms of substituents thereof. Needless to say that these isomers are all included in the compounds in accordance with this invention. Needless to say that arbitrary mixture of isomers thereof is also included by the compound in accordance with this invention.

Because the compound of this invention have glucokinase activation action, it is useful as therapeutic drug and/or prevnetive drug of diabetes cases, moreover, as therapeutic drug and/or prevnetive drug of diabetic complications.

Wherein, diabetic complications are diseases that develop as a result of diabetes mellitus, and as said diabetic complications, for example diabetic nephropathy, diabetic retinopathy, diabetic neurosis, diabetic arteriosclerosis and the like are nominated.

The compound in accordance with this invention can be applited to either type of diabetes mellitus of insulin-dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM).

Moreover, the insulin-dependent diabetes mellitus (IDDM) is considered mainly as adult onset wherein the onset is cuased by addition of insulin resistance due to obesity to the predisposition of hereditary low insulin secretion and insulin resistance inskeletal muscle. Moreover, as for the aforesaid insulin-dependent diabetes mellitus, classifications of type I and type II have been proposed by predisposition thereof.

The compound in accordance with this invention is considered to be useful in type II diabetes mellitus in which the satisfactory lowering of blood glucose level was not thought to be possible with prior art diabetes mellitus drug, in addition to type I insulin-dependent diabetes mellitus.

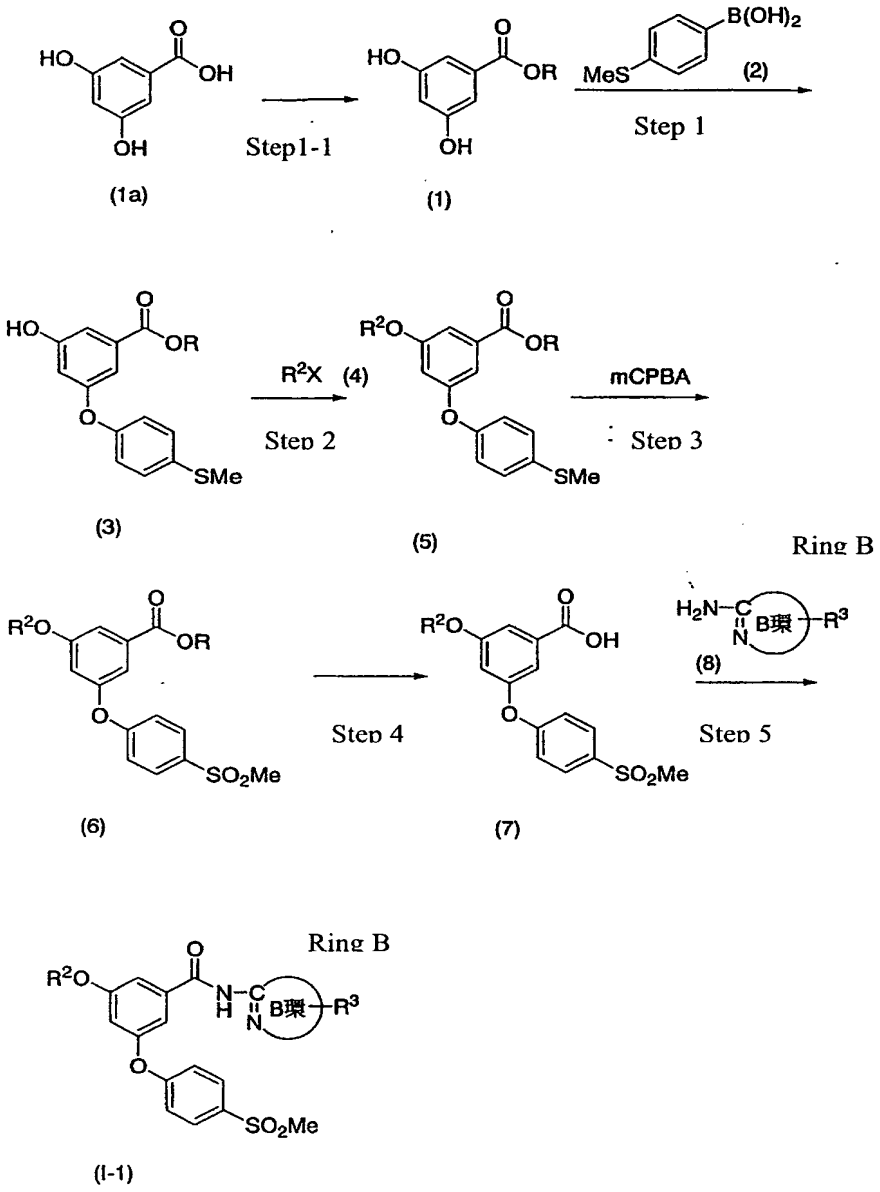
Moreover, in type II diabetes mellitus, the level of postprandial hyperglycemia is maintained over a long period compared to healthy person. However, the compound in accordance with this invention is useful for this type II diabetes mellitus.

Conditions for Carrying Out This Invention

Below, a process for the production of the compound in accordance with this invention is described.

The compound in accordance with this invention (I) can be readily produced by using well known reaction means or by according to itself well-known method. Moreover, as for the compound in accordance with this invention (I) can be produced not only by a synthesis method in ordinary liquid phase, but also by processed using solid phase for example combinatorial synthesis method, parallel synthesis method or the like which have been developed remarkably in reccent years.

The compound in accordance with this invention can be produced preferably using for example following process.



(wherein, R denotes a lower alkyl group, and X denotes a halogen atom, and the other symbol have the same aforesaid definition).

(Step 1-1).

This step comprises a process to produce compound (1) by introducing protecting group to the carboxyl group having 3,5-dihydrobenzoic acid (1a). The protecting group R of the carboxyl group

having compound (1) may be any species as long as it acts as protecting group of carboxyl group in Steps 1-3 and can be readily eliminated in Step 4, and for example lower alkyl group having branched or straight chain such as methyl group, ethyl group, tert-butyl group and the like, halogenated lower alkyl group such as 2-ethyl iodide group, 2,2,2-trichloroethyl group and the like, lower alkenyl group such as allyl group, 2-propenyl group, 2-methyl-2-propenyl group and the like, aralkyl group such as benzyl group, PMB group or the like are nominated.

Such introduction and removal process of protecting group R of carboxyl group can be carried out by a process described in literature (for example Protective Groups in Organic Synthesis, T.W. Green, Second Edition, John Wiley & Sons Co, 1991, or the like), a method in accordance with it or combining these and conventional methods.

Compound (1) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystalliaation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 1)
This step comprises a process to produce 5-hydroxy-3-(4-methylthio phenoxy) benzoate (3) by reacting compound (1) and p-methylthio phenyl boric acid (2) in the presence of copper acetate and base.

The quantity of p-methylthio phenyl boric acid (2) is usually 1-10 equivalents, preferably 1-2.5 equivalents per 1 equivalent of compound (1).

It is possible to use copper nitrate other than copper acetate, but copper acetate is more preferred.

The quantity used of copper acetate or copper nitrate is usually 0.1-5 equivalents, preferably 1-1.5 equivalents.

As the base used, for example triethylamine, diisopropyl ethylamine and the like are nominated, and among these, triethylamine is preferred.

The quantity used of base is usually 0-10 equivalents, preferably 4-6 equivalents.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably 15-30°C.

The reaction time in this step is usually 2-48 hours, preferably 12 hours.

Reaction solvent used in this step may be any solvent as long as it does not interfere with the reaction, and for example methylene chloride, acetonitrile, toluene and the like are nominated, among these, dichloromethane is preferred.

Compound (3) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 2)
This step comprises a process to produce compound (5) by reacting compound (3) obtained in the said step 1 and alkyl halide (4) in the presence of base.

As used compound (4), any compound may be used as long as the one producing compound (5) by progressing reaction in this step without interference, and for example ethyl iodide, 2-propyl bromide, cyclopentyl bromide, 2-bromoethanol and the like are nominated, among these, for example, 2-propyl bromide, cyclopentyl bromide are preferred, and 2-propyl bromide is more preferred.

As the quantity used of compound (4), usually 0.5-10 equivalents, preferably 1-3 equivalents per 1 equivalent of compound (3).

As the base used, for example potassium carbonate, diisopropylamine and the like are nominated, and among these, potassium carbonate is preferred.

The quantity used of base is usually 1-10 equivalents, preferably 1.5-3 equivalents.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably 25-40°C.

The reaction time is usually 1-12 hours, preferably 4-8 hours.

The reaction solvent used in this step may be any solvent as long as the one which does not interfere with the reaction, and N,N-dimethylformamide is preferred. Compound (5) obtained in this way can be

isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 3).
This step comprises a process to produce compound (6) by reacting compound (5) obtained in the said step 2 and mCPBA.

Oxidation reaction used in this step can be carried out by a process described in literature (for example, Brown. D et al, Simple pyrimidines. X. The formation and reactivity of 2-, 4-, and 5-pyrimidinyl sulfones and sulfoxides, Journal of the Chemical Society (Section) C: Organic, vol 7, 1967, p568-572), a method in accordance with it or combining these and conventional methods.

The quantity of using mCPBA is usually 2-10 equivalents, preferably 3-4 equivalents per 1 equivalent of compound (5).

The reaction time is usually 10 minutes to 12 hours and preferably 30 minutes to 1 hour.

The reaction temperature is usually –78 - 15°C, preferably 0 - 10°C.

The reaction solvent used in this step may be any solvent as long as the one which does not interfere with the reaction, and for example methylene chloride, chloroform and the like are nominated, among these, chloroform is preferred.

Compound (6) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 4).
This step comprises a process to produce compound (7) by eliminated protecting group R of the carboxyl group include in compound (6) obtained in the said step 3.

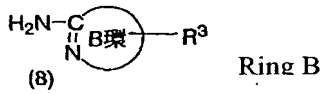
Removal process of protecting group R of carboxyl group can be carried out by a process described in aforesaid literature (for example Protective Groups in Organic Synthesis, T.W. Green, Second Edition,

John Wiley & Sons Co, 1991, or the like), a method in accordance with it or combining these and conventional methods.

Compound (7) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 5).

This step comprises a process to produce compound (1-1) in accordance with this invention by reacting amino compound represented by following formula (8)



(8) Ring B

(wherein, each symbol has the same aforesaid definition) with compound (7) obtained in the said step 4.

As for this reaction, ordinary amide formation reaction may be carried out by a process described in literature (Comprehensive Organic Synthesis, Vol 6, Pergamon Press Co. 1991 and the like), a method in accordance with it or combining these and conventional methods. In other words, it can be carried out by using well-known condensation agent for a person skilled in the art, or by the ester activation method, mixed acid anhydride method, acid chloride method, carbodiimide method and the like which can be used for a person skilled in the art.

As such amide forming reagent, for example thionyl chloride, oxalyl chloride, N,N-dicyclohexylcarbodiimide, 1-methyl-2-bromo pyridinium iodide, N,N'-carbonyldiimidazole, diphenyl phosphoryl chloride, diphenyl phosphoryl azide, N,N'-disuccinimidyl carbonate, N, N'-disuccinimidyl oxalato, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, ethylchloroformate, chloro formic acid isobutyl ester or benzo tri azo-1-yl-oxy-tris (dimethylamino) phosphonium hexafluoro phosphate and the like are nominated, among these, for example thionyl chloride, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, N,N-dicyclohexylcarbodiimide or benzo tri azo-1-yl-oxy-tris (dimethylamino) phosphonium hexafluoro phosphate and the like are ideal. Moreover, in amide forming reaction, base, condensation assistant may be used together with the aforesaid amide forming reagent.

As the base used, for example tertiary aliphatic amine such as trimethylamine, triethylamine, N,N-diisopropyl ethylamine, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0] undeca-7-en (DBU), 1,5-azabicyclo[4.3.0] nona-5-en (DBN) or the like, for example aromatic amine such as pyridine, 4-dimethylaminopyridine, picoline, lutidine, quinoline or in quinoline or the like are nominated, among these, for example tertiary aliphatic amine or the like is preferred, and in particular for example triethylamine, N,N-diisopropyl ethylamine or the like is ideal.

As the condensation assistant used, for example N-hydroxybenzotriazole hydrate, N-hydroxy succinimide, N-hydroxy-5-norbornene-2,3-dicarboximide or 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazole and the like are nominated, among these, for example N-hydroxybenzotriazole or the like is ideal.

The quantity of used compound (8) differs depending on the species of the compound and solvent used and other reaction conditions, however, usually 0.1-10 equivalents, preferably 0.5-3 equivalents with respect to 1 equivalent of carboxylic acid derivative (7) or reactive derivative thereof.

The quantity of using amide forming reagent differs depending on the species of compound and solvent used and other reaction conditions, however, usually 1-10 equivalents, preferably 1-3 equivalents with respect to 1 equivalent of carboxylic acid derivative (7) or reactive derivative thereof.

The quantity of using condensation assistant differs depending on the species of compound and solvent used and other reaction conditions, however, usually 1-10 equivalents, preferably 1-3 equivalents with respect to 1 equivalent of carboxylic acid derivative (7) or reactive derivative thereof.

The quantity of base used differs depending on the species of compound and solvent used and other reaction conditions, however, usually 1-10 equivalents, preferably 1-5 equivalents.

As the reaction solvent used in this step, for example inert solvent is nominated, and it is not restricted in particular so long as not to cause hindrance in the reaction, however, in an embodiment, for example methylene chloride, chloroform, 1,2-dichloroethane, N,N-dimethylformamide, ethyl acetate ester, methyl acetate, acetonitrile, benzene, xylene, toluene, 1,4,-dioxane, tetrahydrofuran, dimethoxyethane or a mixed solvent thereof is nominated, and from the point of ideal reaction temperature security, for example methylene chloride, chloroform, 1,2-dichloroethane, acetonitrile, N,N-dimethylformamide and the like are preferred.

Usually reaction temperature in this step is -78°C to boiling point of solvent temperatures, preferably 0-30°C.

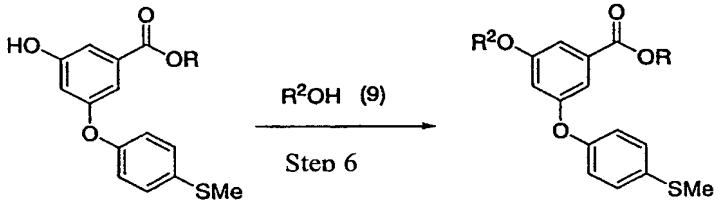
The reaction time in this step is usually 0.5-96 hours, preferably 3-24 hours.

Base, amide formation reagent, condensation assistant used in this step can be used by combining one species of more.

When substituent R3 on B ring of compound (1-1) produced in this step is having protecting group, it is possible to be eliminated the aforesaid protecting group in accordance with requirements. The aforesaid elimination of protecting groups can be carried out by a process described in literature (Protective Groups in Organic Synthesis, T.W. Green, Second Edition, John Wiley & Sons Co, 1991, or the like), a method in accordance with it or combining these and conventional methods.

The compound (1-1) obtained in this way in accordance with this invention can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, crystallisation, solvent extraction, reprecipitation, chromatography and the like.

Moreover, compound (5) produced in the said step 3 can be produced also by the following process.



(3) (5)

(wherein, each symbol has the same the aforesaid definitions).

(Step 6).
This step comprises a process to produce compound (5) by reacting compound (3) produced in the said step 1 and alcohol compound (9).

This reaction is so-called Mitsunobu Reaction, and can be carried out by a process described in

literature (for example The use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products, Synthesis, Vol 1, 1981, pl-28, written by Mitsunobu. O), a method in accordance with it or combining these and conventional method in the presence of the phosphine compound and azo compound.

The quantity of alcohol compound (9) used in this step is usually 0.5-10 equivalents, preferably 1-3 equivalents per 1 equivalent of compound (3).

As the phosphine compound used in this step, usually for example triphenylphosphine, triethylphosphine and the like are nominated.

Usually the quantity of the phosphine compound used is 0.5-10 equivalents, preferably 1-3 equivalents per 1 equivalent of compound (3).

As the azo compound used, for example diethylazo dicarboxylate, diisopropyl azo dicarboxylate and the like are nominated.

The quantity of using azo compound is usually 0.5-10 equivalents, preferably 1-3 equivalents per 1 equivalent of compound (3).

The reaction time in this step is usually 1-48 hours, preferably 4-12 hours.

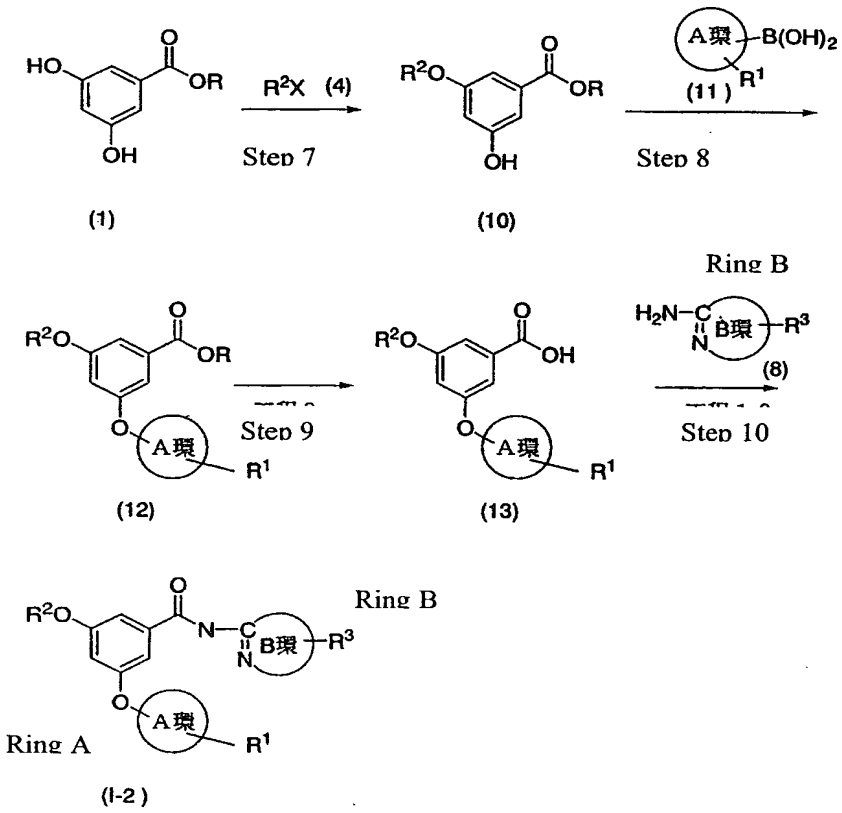
Reaction temperature in this step is usually 0°C to reflux temperature of reaction solvent, preferably 15-30°C.

As the reaction solvent used in this step, it is not restricted in particular so long as the one which does not hinder the reaction. However, in an embodiment, for example tetrahydrofuran, toluene and the like are nominated.

The compound (1-1) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

Moreover, the compound (1-2) in accordance with this invention can be produced also by a process of

following formula.



(wherein, each symbol has the same the aforesaid definitions).

(Step 7).

This step comprises a process to produce compound (10) by reacting compound (1) obtained in the said step and compound (4).

This reaction may be carried out by the same process of the said step 2.

As the reaction conditions such as Equivalent quantity of halogen alkyl compound (4) with respect to compound (1), reaction temperature, reaction time or the like, the reaction can be carried out by the method of aforesaid 2, or a method in accordance with this or in combination of these and conventional methods.

(Step 8).

This step is a process to produce compound (12) by reacting compound (10) obtained in the said step 7 and a boric acid derivative represented by following formula (II)

Ring A 

(11)

(wherein, each symbol has the same the aforesaid definitions).

When a protecting group is required in R1, necessary protecting group corresponding to the kind of R1 can be introduced. The said protecting group of R1 can be any group as long as the group acts as the protecting group of R1 in steps 8-10, thereafter can be easily eliminated and the compound (1-2) in accordance with this invention can be obtained.

The introduction and emilination methods of protecting group of said R1 can be carried out by processes in accordance with literature (for example Protective Groups In Organic Synthesis, T.W. Green, Second Edition, John Wiley & Sons Co, 1991 year, or the like), processes in accordance with these or combining these and conventional methods.

Moreover, R1 can be formed by converting substituent R11 on A ring.

The conversion from substituent R11 on A ring to R1 can be carried out by processes in accordance with literature (for example Comprehensive Organic Synthesis, Vol. 6, Pergamon PressCo, 1991, Comprehensive Organic Transformations, Richard L. et al., VCH Publishers Co, 1988 year, or the like); processes in accordance with these or combining these and conventional methods.

As R11, for example formyl group, halogen atom, alkoxycarbonyl group and the like are nominated.

When R11 is for example formyl group, it can be converted to hydroxymethyl group by reducing the formyl group. As the conversion reaction from formyl group to hydroxymethyl group, a comp having hydroxymethyl group as R1 can be produced by reacting the compound having formyl group and sodium borohydride.

Moreover, the compound having hydroxymethyl group as R1 can be converted into aminomethyl group by azide formation and subsequent reductive reaction.

Moreover, as the conversion reaction from alkoxycarbonyl group to alkylcarbamoyl group, the compound having alkoxycarbonyl group is hydrolysed and thereafter is subjected to amide formation with alkylamine, and thereby the compound having alkylcarbamoyl group as R1 can be produced.

As boric acid derivative represented by the aforesaid formula (II), for example 4-bromo-phenyl boric acid, 4-fluoro-phenyl boric acid, 4-methyl-phenyl boric acid, 4-methoxy-phenyl boric acid, 4-trifluoromethyl-phenyl boric acid, 4-hydroxymethyl-phenyl boric acid, 4-acetyl-phenyl boric acid, 4-cyano-phenyl boric acid, 4-methoxycarbonyl-phenyl boric acid, 4-carboxy-phenyl boric acid, 4-formyl-phenyl boric acid, 4-aminomethyl-phenyl boric acid, 4-carbamoyl-phenyl boric acid and the like are nominated.

When phenyl boric acid derivative represented by the aforesaid formula (II) is having R11 on A ring as substituent, R11 is optionally having a protecting group.

As far as introduction process of the said protecting group is concerned, a process in accordance with literature (Protective Groups in Organic Synthesis, Second eddition, written by T.W. Green, John Wiley & Sons Co., 1991 or the like), a method in accordance with it or combining these and conventional method can be carried out.

The compound obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 9)
This step comprises a process to eliminate protecting group R of the carboxyl group contained in compound (12) obtained in the said step 8. This step can be carried out by the same reaction conditions of the said step 4, using a process in accordance with aforesaid literature (for example Protective Groups in Organic Synthesis, written by T.W. Green, Second Edition, John Wiley & Sons Co, 1991, or the like), a method in accordance with it or combining these and conventional methods.

Compound (13) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being

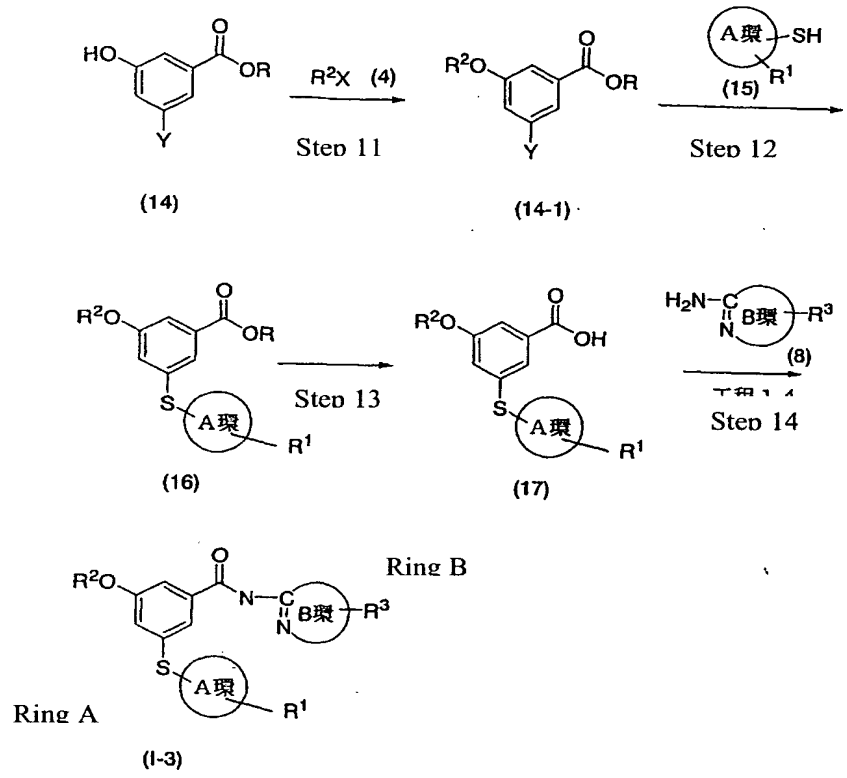
isolated and purified.

(step 10)

This step comprises a process to produce the compound (I-2) in accordance with this invention by reacting compound (13) obtained in the said step 9 and amino compound (8). This reaction can be carried out by the same reaction conditions of the said step 5.

The compound (I-2) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like.

The compound (I-3) in accordance with this invention can be produced also by the following process.



(wherein, Y denotes a halogen atom, and the other symbol have the same aforesaid definition).

(Step 11)

This step comprises a process to produce the compound (14-1) by reacting compound (14) and the said compound (4). In this step, reaction conditions such as equivalent quantity, reaction temperature, reaction solvent or the like of used compound (4) with respect to 1 equivalent of phenol derivative (14) is the same as in aforesaid step 7.

The compound obtained in this way (14-1) can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 12)
This step comprises a process to produce compound by reacting compound (14-1) obtained in the said step 11 and compound (15).

This reaction can be carried out by reacting compound (14-1) and mercapto derivative (15) in the presence of base, hydroquinone and copper bromide.

As the base uses in this reaction, potassium carbonate, cesium carbonate, sodium hydride and the like are nominated, among these, potassium carbonate, sodium hydride are preferred.

The quantity of base used in this step is usually 0.5-20 equivalents, preferably 3-10 equivalent with respect to 1 equivalent of compound (14-1).

The quantity of hydroquinone used in this step is usually 0.1-10 equivalents, preferably 0.2-1.5 equivalents with respect to 1 equivalent of compound (14-1).

The quantity of copper bromide used in this step is usually 0.1-10 equivalents, preferably 0.2-2 equivalents with respect to 1 equivalent of compound (14-1).

The reaction temperature is usually 25°C to reflux temperature of reaction solvent, and preferably 50°C to reflux temperature of reaction solvent.

The reaction time is usually 10 minutes-24 hours, preferably 15 minutes-3 hours.

As the reaction solvent used in this step is not restricted in particular so long as the reaction is not

hindered, however, in an embodiment, for example N,N-dimethylformamide is preferred.

Compound (16) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 13)
This step comprises a process to produce compound (17) by eliminating protecting group of the carboxyl group contained in compound (16) obtained in the said step 12.

This step can be carried out using the same process of the said step 4 or 9 by a process in accordance with literature (for example Protective Groups in Organic Synthesis, written by T.W. Green, Second Edition, John Wiley & Sons Co, 1991, or the like), a method in accordance with it or combining these and conventional methods.

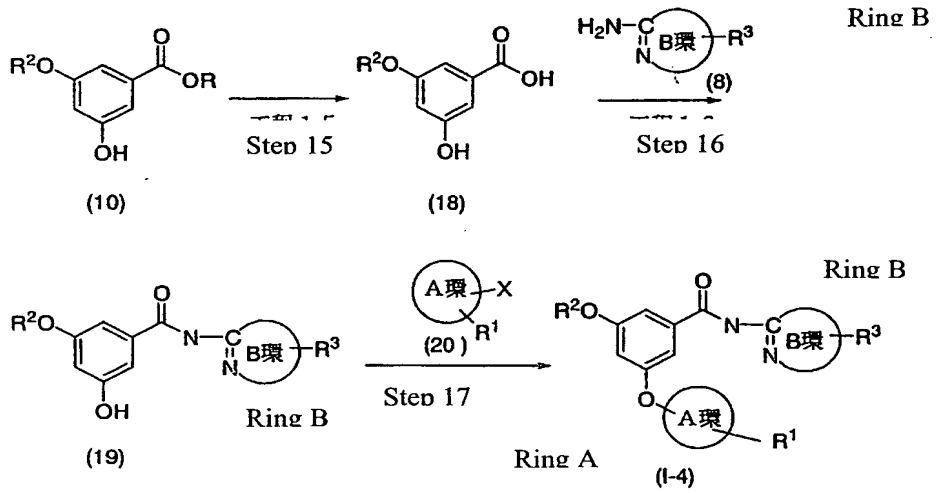
Compound (17) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 14)
This step comprises a process to produce the compound in accordance with this invention (I-3) by reacting compound (17) obtained in the said step 13 and compound (8).

This reaction is an amide bond forming reaction, and reaction conditions such as reaction temperature, reaction solvent or the like is the same as in the said step 5 or 10.

The compound (I-3) in accordance with this invention obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like.

Moreover, the compound (I-4) in accordance with this invention can be produced also by the following process.



(wherein, each symbol has the same the aforesaid definition).

(Step 15)

This step comprises a process to eliminate a protecting group of the carboxyl group contained in compound (10) obtained in the said step 7.

This step can be carried out by the same reaction conditions of the said step 4 by a process in accordance with aforesaid literature (for example Protective Groups in Organic Synthesis, written by T.W. Green, Second Edition, John Wiley & Sons Co, 1991, or the like), a method in accordance with it or combining these and conventional methods.

The compound obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 16)

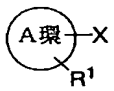
This step comprises a process to produce compound (19) by reacting compound (18) obtained in the said step 15 and compound (8). This reaction is an amide bond forming reaction and can be carried out in the same reaction conditions such as reaction temperature, reaction solvent or the like in the said step 5 or 10.

Compound (19) in accordance with this invention obtained in this way can be isolated and purified

using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 17)

This step comprises a process to produce the compound (I-4) in accordance with this invention by reacting compound (19) obtained in the said step 16 and halogen compound represented by following formula (20)

Ring A 

(20)

(wherein, A ring denotes pyridine ring, pyrazine ring, pyrimidine ring or pyridazine ring, and each symbol has the same aforesaid definitions) in the presence of base.

The quantity of halogen compound (20) used in this step is usually 0.5-10 equivalents, more preferably 1-3 equivalents per 1 equivalent of compound (19).

As the base used in this reaction, potassium carbonate, cesium carbonate, sodium hydride and the like are nominated, among these, potassium carbonate is preferred.

The quantity of base used in this step is usually 0.5-20 equivalents, preferably 1-10 equivalent per 1 equivalent of compound (19).

The reaction temperature is usually 25°C to reflux temperature of reaction solvent, and preferably 50°C to reflux temperature of reaction solvent.

The reaction time is usually one hour to 48 hours and preferably one hour to 24 hours.

As the reaction solvent used in this step, it is not restricted in particular so long as no hindrance in reaction. However, in an embodiment, for example N,N-dimethylformamide is preferred.

In a case to require a protecting group in R1, it is possible to introduce necessary protecting group corresponding to the type of R1.

Protecting group of said R1 may be any group so long as to act as protecting group of R1 in step 17 and thereafter said protecting group is readily eliminated.

Introduction and removal process of protecting group of R1 can be carried out by process in accordance with literature (for example Protective Groups in Organic Synthesis, written by T.W. Green, Second Edition, John Wiley & Sons Co, 1991, or the like), a method in accordance with it or combining these and conventional methods.

Moreover, R1 can be formed by transforming substituent R11 on A ring.

Conversion from substituent R11 on A ring to R1 can be carried out by process in accordance with literature (for example Comprehensive Organic Synthesis, Vol. 6, Pergamon Press Co, 1991, Comprehensive Organlc Transformation, written by Richarrd L. et al., VCH Publishers Co., 1998 or the like), a method in accordance with it or combining these and conventional methods.

As R11, for example halogen atom, alkoxycarbonyl group and the like are nominated.

When R11 is for example alkoxycarbonyl group, it can be converted to hydroxymethyl group by reducing alkoxycarbonyl group.

As for the transformation from alkoxycarbonyl group to hydroxymethyl group, the compound having hydroxymethyl group can be produced as R1 by reacting the compound having alkoxycarbonyl group and lithium aluminium hydride.

Moreover, it is possible to transform the compound having hydroxymethyl group as R1 into aminomethyl group by azide formation and subsequent reductive reaction.

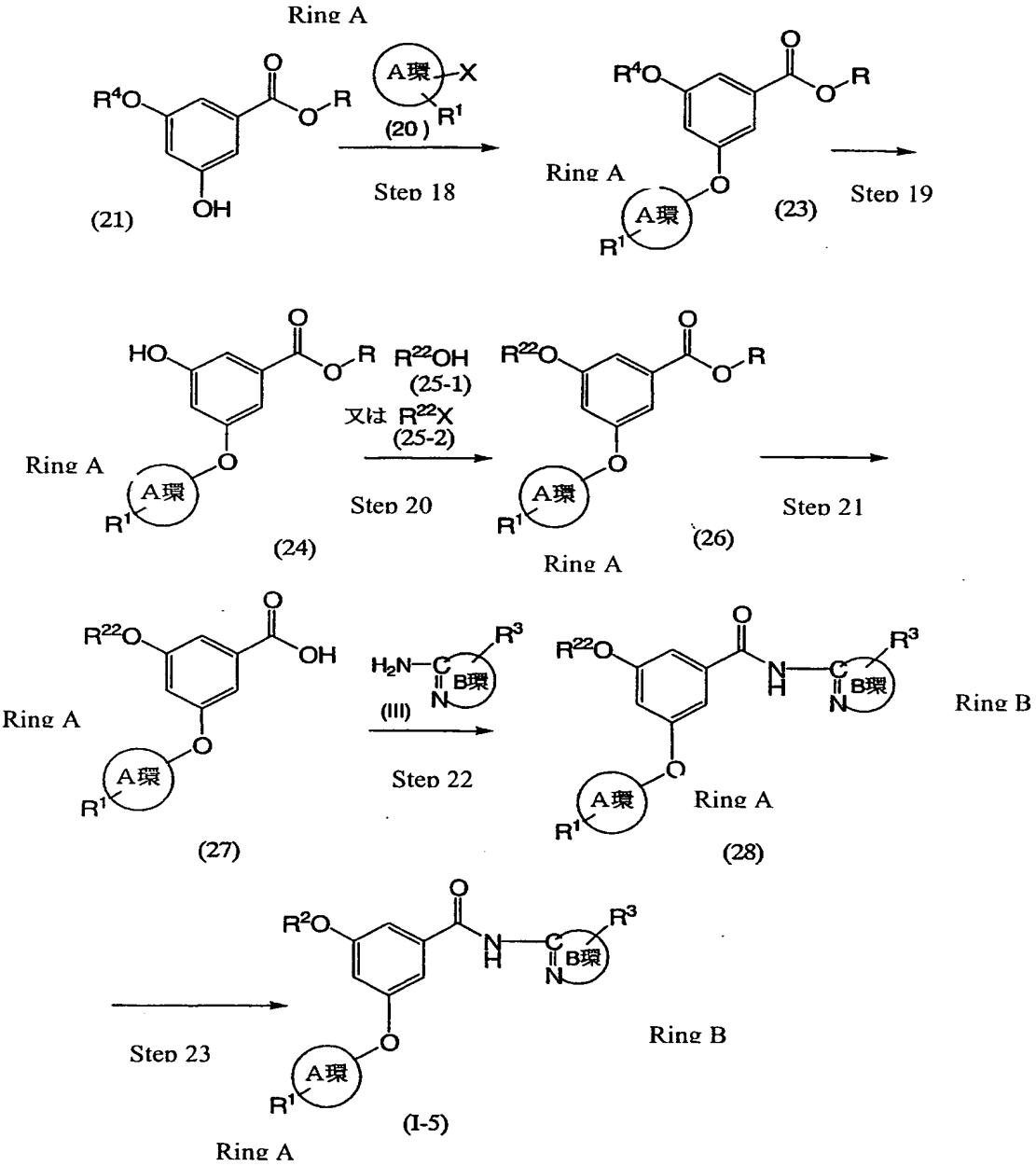
When halogen compound (20) represented by the aforesaid formula is having R11 on A ring as substituent, R11 is optionally having a protecting group.

Introduction process of the said protecting group can be carried out by process in accordance with literature (Protective Groups In Organic Synthesis, T.W. Green, Second Edition, John Wiley & Sons Co, 1991, or the like), a method in accordance with it or combining these and conventional methods.

The compound (I-4) obtained in this way can be isolated and purified using well known separation and

refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like.

The compound in accordance with this invention (I-5) can be produced by the following process.

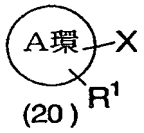


(wherein, R22 denotes R2 optionally having a protecting group, and each symbol has the same

aforesaid definitions).

(Step 18)

This step comprises a process to produce compound (23) by reacting the compound (21) and halogen compound represented by aforesaid formula (20)

Ring A 

(20)

(wherein, R4 denotes a protecting group of hydroxy group, and each symbol has the same aforesaid definitions) in the presence of a base.

Introduction of protecting group R4 of the hydroxy group contained in compound (21) used in this step can be carried out by a literature described above (for example Protective Groups in Organic Synthesis, T.W. Green, Second Edition, John Wiley & Sons Co, 1991, or the like), a method in accordance with it or combining these and conventional methods.

This step can be carried out by the same process of the said step 17, a process in accordance with it or a process combining these and the conventional method.

In a further embodiment as R4, for example, methoxy methyl group, benzyl group, 4-methoxy-benzyl group, 2-(trimethylsilyl) ethoxymethyl group, tert-butyldimethylsilyl group, tert-butyl carbonyl group and the like are nominated.

The quantity of used compound (20) differs depending on the species of compound and solvent, and other reaction conditions, however, usually 0.1-20 equivalents, preferably 0.5-5 equivalents per 1 equivalent of compound (21).

The quantity of base used differs depending on the species of compound and solvent, and other reaction conditions, however, usually 0.1-20 equivalents, preferably 0.5-5 equivalents.

As the base used, any kind of one may be used so long as producing compound (23) in reaction of compound (20) and compound (21) in this step, but for example cesium carbonate, sodium carbonate, potassium carbonate, potassium phosphate, potassium acetate, potassium-tert butyrate, triethylamine and the like are nominated.

As the reaction solvent used, inert solvent is nominated, and it is not restrictied in particular so long as the reaction is not hindered. However, in an embodiment, for example, pyridine, toluene, 1,4,-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like are nominated.

In this step, copper oxide (1), copper oxide (II) or copper chloride (1) may be copresented in the reaction system.

Moreover, in this step, ligand for example palladium salt such as palladium acetate (II) or palladium chloride (II) or the like and 2-(di-tert-butylphosphino) biphenyl or triphenyl phosphine and the like may be copresented in the reaction system.

Moreover, in this step, silver carbonate, silver acetate, silver oxide or trifluoroacetic acid silver may be copresented in the reaction system.

Reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably room temperature to 150°C in this step.

The reaction time in this step is usually 0.1 hour to 72 hours, preferably 30 minutes to 5 hours.

Compound (23) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 19)
This step comprises a process to produce compound (24) by eliminating protecting group of hydroxy group of compound (23) obtained in the said step 18.

Elimination of protecting groups in this step can be carried out by a process in accordance with literature (for example Protective Groups in Organic Synthesis, T.W. Green, Second Edition, John Wiley & Sons Co, 1991, or the like), a method in accordance with it or combining these and conventional method, and whenn R4 is methoxy methyl group, said elimination of protecting groups can be carried out by, for example, using trifluoroacetic acid (TFA), hydrochloric acid.

When TFA is used to eliminate R4, the quantity of TFA is usually 0.5-1000 equivalents, preferably 1-100 equivalents.

When hydrochloric acid is used to elominate R4, the quantity of hydrochloric acid is usually 0.5-1000 equivalents, preferably 1-100 equivalents.

Reaction solvent used in this step is not restricted in particular so long as the reaction is not hindered. However, for example methylene chloride, chloroform, methanol, 1,4,-dioxane and the like are nominated.

Usually the reaction temperature is 0°C to the reflux temperature of the solvent, preferably room temperature to reflux temperature of reaction solvent.

The reaction time is usually 0.1 hour-72 hours, preferably 30 minutes-12 hours.

Compound (24) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 20)
This step comprises a process to produce compound (26) by reacting compound (24) obtained in aforesaid step and the compound (25-1) or (25-2).

The reaction of compound (24) and compound (25-1) is so-called Mitsunobu Reaction, and it can be carried out by process in accordance with literature (written by Mitsunobu O, The use of diethyl azodicarboxylate and triphenylphosphineln synthesis and transformation of natural products, Synthesis, Vol. 1, 1981, p1-28), a method in accordance with it or combining these and conventional method in the presence of the phosphine compound and azo compound.

The quantity of alcohol compound (25-1) used in this step is usually 0.5-10 equivalents, preferably 1-3 equivalents per 1 equivalent of compound (24). As the phosphine compound used in this step, usually for example triphenylphosphine, triethylphosphine and the like are nominated.

Usually the quantity of the using phosphine compound is 0.5-10 equivalents, preferably 1-3 equivalents per 1 equivalent of compound (24).

As the azo compound used, for example diethylazo dicarboxylate, diisopropyl azo dicarboxylate and the like are nominated.

The quantity of using azo compound is usually 0.5-10 equivalents, preferably 1-3 equivalents per 1 equivalent of compound (24).

The reaction time in this step is usually 1-48 hours, preferably 4-12 hours.

Reaction temperature in this step is usually 0°C to reflux temperature of reaction solvent, preferably 15-30°C.

As the reaction solvent used in this step, it is not restricted in particular so long as the reaction is not hindered. However, in an embodiment, for example tetrahydrofuran, toluene and the like are nominated.

Moreover, the reaction of compound (24) and compound (25-2) can be carried out by the same process as in the aforesaid step 2.

Reaction conditions such as equivalent quantity of halogen compound (25-2) with respect to compound (24), reaction temperature, reaction time or the like can be carried out by the same conditions as in aforesaid 2, a method in accordance with it or combining these and conventional methods.

Furthermore, compound (26) can be produced by reacting the compound (24) and compound represented by formula (25-3)

$$R^{22}\text{-}X^{3} \quad (25\text{-}3)$$

(wherein, R22 denotes R2 optionally having a protecting group, and X3 denotes leaving group such as mesylate or tosylate or the like).

Reaction conditions such as equivalent quantity of the compound (25-3) with respect to the compound (24), reaction temperature, reaction time or the like can be carried out by the same conditions as in aforesaid 2, a method in accordance with it or combining these and conventional methods.

Compound (26) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 21)
This step comprises a process to produce compound (27) by eliminating protecting group R of the carboxyl group contained in compound (26) obtained in the said step.

This step can be carried out by the same reaction conditions of the said step 4 by a process in accordance with aforesaid literature (for example Protective Groups in Organic Synthesis, T.W. Green, Second Edition, John Wiley & Sons Co, 1991, and the like), a method in accordance with it or combining these and conventional methods.

Compound (27) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 22)
This step comprises a process to produce compound (28) by reacting compound (27) obtained in the said step and amino compound (III).

This reaction is an amide bond forming reaction, and it can be carried out in the same reaction conditions such as reaction temperature, reaction solvent or the like as in the said step 5, 10.

Compound (28) in accordance with this invention obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like.

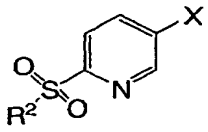
When R22 of compound (28) is not having protecting group, compound (28) is equivalent to the compound in accordance with this invention.

Moreover, when protecting group is contained in R22 and/or R3 of compound (28), the compound in accordance with this invention (1-5) is possible to produce by eliminating the protecting group.

Elimination of protecting groups can be carried out by a process in accordance with literature (for example Protective Groups in Organic Synthesis, T.W. Green, Second Edition, John Wiley & Sons Co, 1991, and the like), a method in accordance with it or combining these and conventional methods.

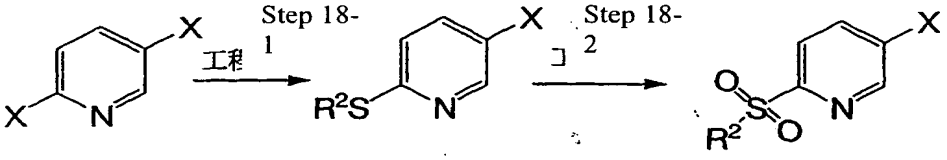
For example, in a case that protecting group is required, when having hydroxy group as substituent on R2, as protecting group of hydroxy group, for example, tert-butyldimethylsilyl group and the like are nominated, and as said elimination of protecting groups, hydrochloric acid, trifluoroacetic acid, sodium hydroxide, tetrabutyl ammonium fluoride and the like are nominated.

Moreover, as one of compound (20) used in step 18, for example, the compound represented by following formula (22)



(22)

(wherein, each symbol has the same the aforesaid definition) is nominated, and the said compound can be produced using the process shown as follows.



(22-1) (22-2) (22)

(each symbol is same as in the aforesaid definition).

(Step 18-1)

This step comprises a process to produce alkyl sulphanyl pyridines (22-2) by reacting dihalo pyridine compound (22-1) and sodium thio alkoxide.

As the dihalo pyridine used in this step, in an embodiment, for example, 2,5-dibromo pyridine, 2,5-dichloropyridine, 2,5-diiodo pyridine, 5-bromo-2-chloropyridine, 2-chloro-5-iodopyridine, 5-bromo-2-fluoropyridine and the like are nominated.

Usually sodium thio alkoxide used in this step is usually 0.1-3 equivalents, preferably 1-2 equivalents with respect to 1 equivalent of compound (22-1).

As the sodium thio alkoxide used, in an embodiment, for example, sodium thio methoxide, sodium thio ethoxide and the like are nominated.

As the solvent used in this step, for example inert solvent is nominated, and it is not restricted in particular so long as reaction is not hindered. However, in an embodiment, for example N,N-dimethylformamide, tetrahydrofuran, 1-methyl-2-pyrrolidinone, water and the like are nominated.

The reaction time of this step is usually 30 minutes to 72 hours and preferably one hour to 12 hours.

The compound (22-2) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 18-2)
This step comprises a process to produce compound (22) by reacting compound (22-2) obtained in the said step 18-1 and mCPBA.

Oxidation reaction which is used in this step can be carried out by the same method as in step 3, a method in accordance with it or a process combining of these and the conventional method.

Also, as for the quantity of mCPBA, reaction temperature, the reaction time, the reaction solvent used in this step, it is possible to use the same method as in step 3 or the process in accordance with this.

Furthermore, as the oxidant used in this step, hydrogen peroxide water, sodium tungstate, sodium hypochlorite and the like are nominated.

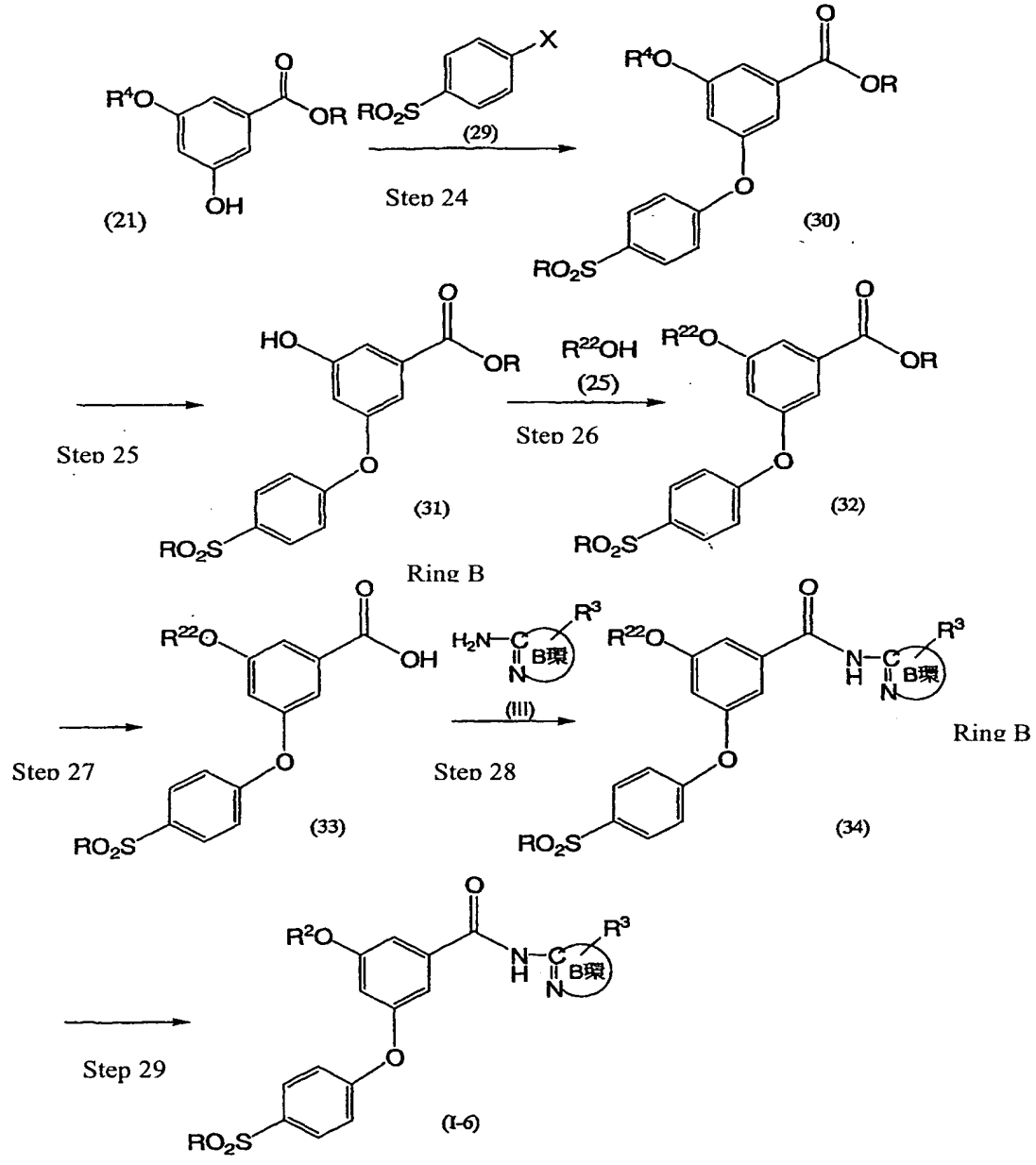
As the quantity of oxidant used in this step, usually it is 0.1-10 equivalents, preferably 1-5 equivalents with respect to 1 equivalent of compound (22-2).

As the solvent used in this step, there is no restrictions in particular so long as the reaction is not hindered, however, in an embodiment, acetonitrile, ethanol, methanol and the like are nominated.

Compound (22) obtained in this way can be isolated and purified using well known separation and

refinement means, for example concentration, vacuum concentration, crystallisation, solvent extraction, reprecipitation, chromatography and the like.

The compound in accordance with this invention (1-6) can be produced also by the following process.



(wherein, each symbol has the same the aforesaid definition).

(Step 24)
This step is a process to produce compound (30) by reacting compound (21) and compound (29) in the presence of base.

As X which contained in compound (29) used in this step, among halogen atom of the said definition, in a further embodiment, for example bromine atom and iodine atom are preferred.

As the R which contained in compound (29) used in this step, among lower alkyl group of the said definition, it is preferably in a further embodiment, for example methyl group of ethyl group, propyl group, isopropyl group and the like.

As the base used in this step, potassium phosphate, potassium acetate, potassium-tert butyrate, triethylamine and the like are nominated.

The quantity of base used in this step is usually 0.01-10 equivalents, preferably 0.1-2 equivalents per 1 equivalent of compound (21).

Moreover, in this step, ligand for example palladium salt such as palladium acetate (II), palladium chloride (II) or the like and 2-(di-tert-butylphosphino) biphenyl or triphenyl phosphine and the like may be copresented in the reaction system.

The quantity of palladium salt used in this step is usually 0.01-10 equivalents, preferably 0.1-2 equivalents per 1 equivalent of compound (21).

The quantity of ligand used in this step is usually 0.1-10 equivalents, preferably 0.5-2 equivalents with respect to compound (21).

Usually the reaction temperature is room temperature to reflux temperature of reaction solvent and preferably 50°C to reflux temperature of reaction solvent.

The reaction solvent may be used any solvent so long as the one no hindrance for the reaction, but for example, toluene, 1,4,-dioxane, N,N-dimethylformamide, tetrahydrofuran, 1-methyl-2-pyrrolidinone and the like are nominated.

The reaction time is usually 30 minutes to 72 hours and preferably one hour to 12 hours.

Compound (30) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 25)
This step comprises a process to produce compound (31) by eliminating the R4 which is a protecting group of hydroxy group of compound (30) obtained in the said step 24.

Elimination reaction of hydroxy group of (30) can be carried out by a process in accordance with the aforesaid literature (for example Protective Groups in Organic Synthesis, T.W. Green, Second Edition, John Wiley & Sons Co, 1991, and the like), a method in accordance with it or combining these and conventional method, and it is produced using the same process of aforesaid step 19, a process in accordance with this or combining these and the conventional method.

Compound (31) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 26)
This step comprises a process to produce compound (32) by reactiog compound (31) obtained in the said step 25 and R22OH.

The reaction which is used in this step is so-called Mitsunobu Reaction, and can be carried out by a process in accordance with aforesaid literature (for example written by Mitsunobu O., The use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products, Synthesis, Vol 1, 1981, p1-28), a method in accordance with it or combining these and conventional method in the presence of the phosphine compound and azo compound.

The quantity of alcohol compound (25) used in this step is usually 0.5-10 equivalents, preferably 1-3 equivalents per 1 equivalent of compound (31).

As the phosphine compound used in this step, usually for example triphenylphosphine, triethylphosphine and the like are nominated.

Usually the quantity of the using phosphine compound is 0.5-10 equivalents, preferably 1-3 equivalents per 1 equivalent of compound (31).

As the azo compound used, for example diethylazo dicarboxylate, diisopropyl azo dicarboxylate and the like are nominated.

The quantity of using azo compound is usually 0.5-10 equivalents, preferably 1-3 equivalents per 1 equivalent of compound (31).

The reaction time in this step is usually 1-48 hours, preferably 4-12 hours.

Reaction temperature in this step is usually 0°C to reflux temperature of reaction solvent, preferably 15-30°C.

As the reaction solvent used in this step, it is not restricted in particular as long as no hindrance in reaction. However, in an embodiment, for example tetrahydrofuran, toluene and the like are nominated.

Compound (32) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 27)
This step comprises a process to produce compound (33) by eliminating a protecting group of the carboxyl group of the aforesaid compound (32).

This step can be carried out by the same process of the said step the 21, a method in accordance with it or combining these and conventional methods.

Compound (33) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction,

crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

(Step 28)
This step comprises a process to produce compound (34) by reacting compound (33) obtained in the said step 27 and the compound represented by formula (III).

Reaction in this step is so-called amide bond forming reaction, and it can be carried out by the same process of the aforesaid step 22, a method in accordance with it or combining these and conventional methods.

Compound (34) obtained in this way can be isolated and purified using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallisation, reprecipitation, chromatography and the like, or provided to the next step without being isolated and purified.

Moreover, in compound (34), when protecting group is not in R3 and/or R22, compound (34) is the compound in accordance with this invention.

(Step 29)
This step comprises a process to produce the compound (I-5) in accordance with this invention, when protecting group is presented in R3 and/or R22 of compound (34) obtained in the said step 28, by suitably eliminating protecting group.

The reaction in this step can be carried out by a process in accordance with the aforesaid literature (for example Protective Groups in Organic Synthesis, T.W. Green, Second Edition, John Wiley & Sons Co, 1991, or the like), a method in accordance with it or combining these and conventional methods.

The compound (I-5) obtained in this way can be isolated and purified by using the well known separation and refinement means, for example concentration, vacuum concentration, crystallisation, solvent extraction, reprecipitation, chromatography and the like.

Heteroaryl carbamoyl benzenes provided by this invention can be present as pharmacologically acceptable salt, and as for the aforesaid salt can be produced in accordance with conventional method using aforesaid formula (I-1), (I-2), (I-3) (I-4), (I-5) and (I-6) included by compound (1) in accordance

with this invention.

In an embodiment, when the compound of aforesaid (I-1), (I-2), (I-3) (I-4), (I-5) and (I-6) has a basic group derived from, for example the amino group, pyridyl group or the like within the aforesaid molecule, it is possible to convert to corresponding pharmacologically acceptable salt by treating the aforesaid compound with acid.

As the aforesaid acid addition salt, the acid addition salt for example hydrogen halide acid salt such as hydrochloride, hydrofluoric acid salt, hydrobromic acid salt, hydroiodic acid salt or the like, inorganic salt such as nitrate, perchlorate, sulfate, phosphate, carbonate or the like, lower alkyl sulfonate such as methanesulfonate, trifluoromethanesulfonate, ethanesulfonic acid salt or the like, aryl sulfonate such as benzensuplhonate, p-toluenesulfonate or the like, organic salt such as fumarate, succinate, citrate, tartrate, oxalate, maleate or the like and organic acid of amino acid such as glutamic acid salt, aspartate or the like are nominated. Moreover, when the compound of this invention is having acidic group in the said group, for example when it has carboxyl groups, it is possible to convert to the corresponding pharmacologically acceptable salt by treating the aforesaid compound with base. As the aforesaid base addition salt, for example alkali metal salt such as sodium, potassium and the like, alkaline earth metal salt such as calcium, magnesium and the like, salt of organic base such as ammonium salt, guanidine, triethylamine, dicyclohexylamine and the like are nominated. Furthermore, the compound of this invention may be present as free compound or arbitrary hydrate or solventate of salts thereof.

In the production of agent for therapy or prevention of symptom or a disease related to type II diabetes mellitus or corresponding thereof, and the compound of formula (I) in accordance with this invention can be used in a combination of the compound of formula (I) and support material.

Of course the dose for therapy or prevention of the compound of formula (I) in accordance with this invention is altered by character of symptom to be treated, the specific compound and administration route to be selected.

Moreover, it is altered also by age, body weight and sensitivity of each patient. Generally dosage per day is about 0.001 mg to 100 mg per 1 kg in weight as the quantity of single administration or a plurality of administrations, and preferably it is about 0.01 mg to 50 mg, more preferably about 0.1 mg to 10 mg per 1 kg in weight. There is a case to be required to use the dose exceeding the range of these restriction.

As example of appropriate quantity of oral administration, as single or plurality of adminstrations of 2-4 times per day, it is at least 0.01 mg and at most 2.0 g. Preferably the range of dose is about 1.0 mg to about 200 mg in administration of once or twice a day. More preferably, the range of dose is about 10 mg to 100 mg in administration of once per day.

When intravenously administration or oral administration is used, typical administration range is about 0.001 mg to about 100 mg (preferably, about 0.01 mg to about 10 mg) of the compound of formula (I) per 1 kg in weight per day, and more preferably about 0.1 mg to 10 mg of the compound of formula (I) per 1 kg in body weight pre day.

As described above, medicinal composition includes the compound of formula (I) and pharmacologically acceptable carrier. The term "a composition" includes also active and inerts component constructed carrier (pharmacologically acceptable excipient) in addition to the one obtained by combining, complexing or agglomerating ny of 2 or more components directly or indirectly, the one obtained by the result of dissociation of one or more component or the one obtained by result of other type action or interaction between components.

A composition containing the compound of formula (I) in an effective quantity for therapy or prevention of type II diabetes mellitus or delaying onset thereof by combining with pharmacologically permitted carrier is preferred.

Any appropriate administration route can be used in order to administer the effective dose of the compound in accordance with this invention to mammal, in particularly human. For example, orally, rectum, locally, vein, eye, lung, nose or the like can be used. As example of administrative form, there are tablet, troche, powder, suspension, solution, encapsulated formulation, cream, aerosol or the like, and tablet for oral is preferred.

In preparation of a composition for oral, any medium can be used so long as an ordinary medium for drug, and for example water, glycol, oil, alcohol, flavor additive, preservative, coloring agent or the like. When liquid composition for oral is prepared, for example suspension, elixir agent and solution are nominated, and as carrier, for example, starch, sugar, microcrystalline cellulose, diluent, granulating agent, lubricant, binding agent, disintegrating agent or the like are nominated. When solid composition for oral is prepared, for example, powder, encapsulated formulation, tablet or the like are nominated, and among these, solid composition for oral is preferred.

From ease of administration, tablet and encapsulated formulation are the most useful oral administration forms. Tablet can be coated with normal aqueous or non-aqueous technique in accordance with requirements.

In addition to the aforesaid ordinary administrative form, the compound in accordance with formula (I) is possible to be administered with release regulation means and/or delivery apparatus in accordance with, for example U.S. patent number 3,845,770, 3,916,899, 3,536,809, 3,598,123, 3,630,200 and 4,008,719.

As for the medicinal composition in accordance with this invention which is suitable for oral administration, it is nominated encapsulated formulation, cashew agent or tablet including active ingredient in a fixed quantity determined beforehand respectively as powder or granule, or as water-soluble liquid, water insoluble liquid, emulsion of oil in water type or emulsion of water in oil type It is possible that such composition is prepared using any kind of process in pharmaceutics, and all processes are included a process to biding together active ingredient and carrier formed from one or more necessary component.

Generally composition is prepared by mixing thoroughly and also uniformly active ingredient and liquid carrier or solid carrier separated well or both of them, and thereafter, making product in suitable form in accordance with requirements. For example, tablet is prepared by compression and molding, together with one or more subcomponent in accordance with requirements. Compression tablet is prepared by compressing active ingredient in form such as powder, granule or the like freely with mixing with binding agent, lubricant, inert excipient, surface active agent or dispersant in accordance with requirements with a suitable machine. Formed tablet is prepared by forming mixture of the wet compound in powder form and diluent of inert liquid with a suitable machine.

Preferably each tablet includes active ingredient about 1 mg to 1 g, and each cashew agent or encapsulated formulation includes active ingredient about 1 mg to 500 mg.

Example of administrative form on drug of the compound of formula (I) is as follows.

Table 1

Suspension for injection (1.M.)

	mg/ml
Compound of formula (I)	10

Methyl cellulose	5.0
Tween 80	0.5
Benzyl alcohol	9.0
Benzalkonium chloride	1.0

It is made 1.0 ml by addition of water for injection.

Table 2

Tablet

	mg/tablet
Compound of formula (I)	25
Methyl cellulose	415
Tween 80	14.0
Benzyl alcohol	43.5
Magnesium stearate	2.5
	Total 500 mg

Table 3

Encapsulated formulation

	mg/capsole
Compound of formula (I)	25
Lactose powder	573.5
Magnesium stearate	1.5
	Total 600 mg

Table 4

Aerosol

	per 1 container
Compound of formula (I)	24 mg
Lecithin, NF Liq. Conc.	1.2 mg
Trichlorofluoromethane, NF	4.025 mg
Dichlorodifluoromethane, NF	12.15 g

The compound of formula (I) can be used by combining other agents used for therapy / prevention / delay of the onset of type II diabetes mellitus in addition to the disease or symptoms related to type II diabetes mellitus. The said other agents can be administered separately or simultaneously with the compound of formula (I) in usually-used administration route and dose.

When the compound of formula (I) is simultaneously used with one or more agent, a medicinal composition containing the compound of formula (I) and these other agents is preferable. Accordingly,

the medicinal composition in accordance with this invention includes one or more other active ingredients in addition to the compound of formula (I). As example of active ingredient used by combining with the compound of formula (I), which may be administered separately or in a same medicinal composition, however, it is not restricted in following species.

(a) bis-guanide (for example, buformin, metformin, phenformin),
(b) PPAR agonist (for example, troglitazone, pioglitazone, nosiglitazone),
(c) Insulin,
(d) Somatostatin,
(e) α-glucosidase inhibitor (for example, Voglibose, miglitol, acarbose) and
(f) Insulin secretion promoter (for example, acetohexamide, carbutamide, chlorpropamide, glibomuride, gliclazide, glimepiride, glipizide, gliquidone, glisoxepid, glyburide, glyhexamide, glypinamide, phenbutamide, tolazamide, tolbutamide, tolcyclamide, nateglinide, repaglinide).

Weight ratio of the compound of formula (I) with respect to the 2nd active ingredient is altered in range of wide restriction, and moreover, it depends on effective dose of each active ingredient. Accordingly for example, when PPAR agonist is used by combining with the compound of formula (I), weight ratio of the compound of formula (I) with respect to PPAR agonist is generally about 1000 : 1-1 : 1000, and preferably about 200 : 1-1 : 200. Combination of the compound of formula (I) and other active ingredient is in the aforesaid range, however, in any case, effective dose of each active ingredient should be used.

Hereinafter glucokinase activated property shown by the compound represented by compound (I) in accordance with this invention and a test process thereof.

Measurement of excellent glucokinase activation action contained in the compound represented by the aforesaid formula (I) can be carried out by a process in accordance with literature (for example Diabetes, vol 45, pp. 1671-1677, 1996, or the like) or a method in accordance with it.

As far as glucokinase activity is concered, glucose-6-phosphoric acid is not directly measured, but degree of activation of glucokinase is determined by measuring the quantity of Thio-NADH formed, when glucose-6-phosphoric acid dehydrogenase, which is the reporter enzyme, forms phospho gluconolactone from glucose-6-phosphoric acid.

Recombinant human liver GK used in this assay was expressed in E.coli as FLAG fusion protein and

refined with ANTIFLAG M2 AFFINITY GEL (Sigma).

The assay was carried out at 30°C using flat bottomed 96-well plate.

Assay buffer (25 mM Hepes Buffer: pH=7.2, 2 mM MgCl2, 1 mM ATP, 0.5 mM TNAD, 1 mM, dithiothreitol) 69 μl was aliquote and DMSO 1 μl was added as DMSO solution of the compound or control. Next, enzyme mixture (FLAG-GK, 20U/ml G6PDH) 20 μl cooled in ice was discharged, and thereafter, the substrate 25 mM glucose 10 μl was added, and reaction was started (the final glucose concentration= 2.5 mM).

After start of reaction, increase of absorbance of 405 nm was measured for ten minutes every 30 seconds, and increment for the first five minutes was used, and evaluation of the compound was carried out. FLAG-GK was added so that absorbance increment after five minutes became between 0.05-0.1 in the presence of 1 % DMSO.

The OD value with DMSO control was made 100 %, and the OD value in each concentration of the test compound was measured.

From the OD value of each concentration, Emax (%) and EC_{50} (μM) were calculated, and these were used as indicators of GK activation property of the compound.

The GK activation property of the compound in accordance with this invention was measured by this method. The results thereof are shown in the following Table 1.

Table 5

(GK activated property of the compounds of this invention).

Compound number	Emax (%)	EC_{50} (μM)
Production Example 1	957	0.25
Production Example 2	84,4	0.08
Production Example 59	936	0.53

As shown in the aforesaid Table 1, the compound in accordance with this invention has an excellent GK activated property with Emax and EC_{50} as indicator.

Ideal form for Carrying Out the Invention

Hereinafter, this invention will be further described in concrete terms by Preparation Examples and Production Examples. However, this invention is not restricted in any way by these.

Preparation Example 1

The 10 pts. of compound of Production Example 1, heavy magnesium oxide 15 pts. and lactose 75 pts. were uniformly mixed and made into powdered drug in powdery-form or fine granular of 350 μm or less. This powder was introduced into capsule container and made into capsules.

Preparation Example 2

The 45 pts. of compound of Production Example 1, starch 15 pts., lactose 16 pts., crystalline cellulose 21 pts., polyvinyl alcohol 3 pts. and distilled water 30 pts. were uniformly mixed and thereafter, pulverised, granulated and dried, and thereafter, made into granule of a diameter size of 1410-177 μm by classification with a sieve.

Preparation Example 3

Granules were produced by the same process as in Preparation Example 2, and thereafter, calcium stearate 3 pts. was added with respect to this granule 96 pts., and tablets of a diameter of 10 mm were produced by compression-molding.

Preparation Example 4

Crystalline cellulose 10 pts. and calcium stearate 3 pts. were added with respect to granule 90 pts. obtained by process of Preparation Example 2, and made a tablet of a diameter of 8 mm by compression-molding, and thereafter, thereto was added syrup gelatin, precipitated calcium carbonate mixed suspension, and sugar-coated tablet was produced.

Hereinafter, this invention will be described in concrete terms by Preparation Examples, Production Examples, Reference Examples furthermore. However, this invention is not restricted in any way by these.

Thin layer chromatograph of Example was used Silicagel 60F245 (Merck) as plate and UV detector as detection method. As silica gel for column, Wakogel TM C-300 (Wako Jyunyaku) and as silica gel for reverse phase column, LC-SORB TM SP-B-ODS (Chemco) or YMC-GEL TM ODS-AQ 120-S50 (Yamamura Chemical Research) were used respectively.

Meaning of abbreviation in the following Examples are shown below.

i-Bu: isobutyl group.

n-Bu: n-butyl group.

t-Bu: t-butyl group.

Me: methyl group.

Et: ethyl group.

Ph: phenyl group.

i-Pr: isopropyl group.

n-P: n-propyl group.

$CDCl_3$: deuterated chloroform.

CD3OD: deuterated methanol.

DMSO-d_6 : heavy dimethyl sulphoxide.

The meaning of abbreviation in nuclear magnetic resonance spectrum are as follows.

s: singlet.

D: doublet.

Dd: double doublet.

t: triplet.

m: multiplet.

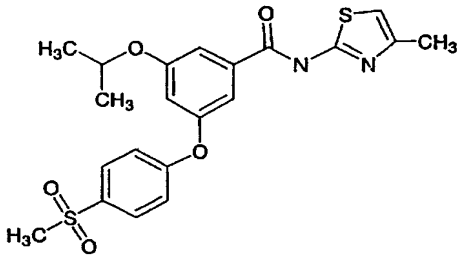
br: broad.

q: quartet.

j: coupling constant.

Hz: Hertz.

Production Example 1.



Preparation of 5-isopropoxy-3-(4-methanesulphonyl phenoxy)-N-(4-methylthiazol-2-yl)-benzamide.

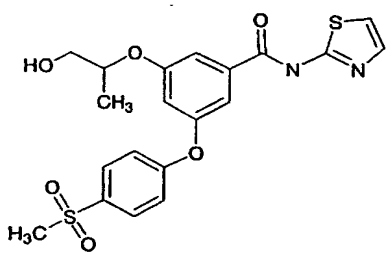
Molecular sieve 4 A 29.0 g, p-methylthio phenyl boric acid 22.0 g (0.13 mol), copper (II) acetate 21.6g (0.13 mol) and triethylamine 83.0 ml (0.59 mol) were added to methylene chloride solution (1.2 L) of 3,5-dihydroxybenzoic acid methyl ester 20.0 g (0.12 mol), and thereafter, it was stirred at room temperature under oxygen atmosphere overnight. The reaction liquor was filtered, thereafter concentrated under reduced pressure. The obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 2 : 1) and 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester 12.4 g (yield = 36 %) were obtained as yellow solid.

Potassium carbonate 129 mg (0.94 mmol) and 2-bromopropane 0.053 ml (0.56 mmol) were added to N,N-dimethylformamide solution (2.5 ml) of the obtained phenol body 54.4 mg (0.19 mmol), and thereafter the reaction liquor was stirred at 80°C for four hours. Water was added to the reaction liquid, extraction was carried out with ethyl acetate, the organic layer was washed with saturated aqueous sodium chloride solution, and after drying, and it was concentrated under reduced pressure. The obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 2 : 1) and thereby 5-isopropoxy-3-(4-methylthiophenoxy)-benzoic acid methyl ester 55.4 mg (yield = 89%) was obtained as a colourless oily substance. Next, m-chloroperbenzoic acid 64.0 mg (0.37 mmol) was added under ice cooling to chloroform solution (2.0 ml) of the obtained ester 41.0 mg (0.12 mmol), and the reaction liquor was stirred under ice cooling for 20 minutes. Sodium thiosulfate aqueous solution was added to the reaction liquor, the organic layer was washed with saturated aqueous sodium bicarbonate solution and then with saturated aqueous sodium chloride solution, and after drying, it was concentrated under reduced pressure. The obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 1 : 1) and thereby 5-isopropoxy-3-(4-methanesulphonyl phenoxy)-benzoic acid methyl ester 43.9 mg (yield = 98%) was obtained as a colourless oily substance.

To methanol solution (1.0 ml) of the obtained sulfone 41.0 mg (0.11 mmol), 2 N sodium hydroxide

aqueous solution 0.28 ml (0.56 mmol) was added, and the reaction liquor was stirred overnight. A 2 N hydrochloric acid aqueous solution was added to the reaction liquid, extraction was carried out with ethyl acetate, the organic layer was washed with saturated aqueous sodium chloride solution, and after drying, it was concentrated under reduced pressure, thereby a crude product of carboxyl body was obtained. 2-amino-4-methylthiazol 5.90 mg (0.51 mol), 1-hydroxybenzotriazole hydrate 9.30 mg (0.068 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride 13.0 mg (0.068 mol) were added to methylene chloride solution (0.5 ml) of the obtained carboxyl body 12.0 mg (0.034 mmol), and thereafter, it was stirred at room temperature overnight. The reaction liquor was concentrated under reduced pressure, the obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 1 : 1) and the title compound was obtained as a white solid. Analysis data of the compound obtained by Production Example 1 are shown below.
^{1}H-NMR ($CDCl_3$) δ :1.34 (6H, d, J = 6.0 Hz), 2.22 (3H, d, J = 0.7 Hz), 3.08 (3H, s), 4.53-4.57 (1H, m), 6.57 (1H, d, J = 0.7 Hz), 6.80 (1H, t, J = 2.0 Hz), 7.11 (1H, d, J = 2.0 Hz), 7.12 (2H, d, J = 8.8 Hz), 7.27 (1H, d, J = 2.0 Hz), 7.92 (2H, d, J = 8.8 Hz).
ESI-MS (m/e) = 447 $(M+H)^+$.

Production Example 2



Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-thiazol-2-yl-benzamide

(2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane 1.40 g (7.40 mmol) and triphenyl phosphine 2.00 g (7.40 mmol) were added to tetrahydrofuran solution (10 ml) of 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester 1.20 g (4.13 mmol) obtained by Production Example 1, and thereafter diethylazo dicarboxylate 3.20 ml (7.40 mmol) was added under ice cooling, and it was stirred at room temperature for two hours. Water was added to the reaction liquid, extraction was carried out with ethyl acetate, the organic layer was washed with saturated aqueous sodium chloride solution, and after drying, and it was concentrated under reduced pressure. The obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 95 : 5) and 5-((1S)-2-(t-butyldimethylsiloxy)-1-methyl-ethoxy)-3-(4-methylthiophenoxy)-benzoic acid methyl ester 1.63 g (yield = 95 %) was obtained as a colourless oily substance. Next, m-chloroperbenzoic acid 2.06 g (12.0 mmol) was added under ice cooling to chloroform solution (40 ml) of the obtained ester 1.84 g (3.97 mmol), and the reaction liquor was stirred under ice cooling for 30

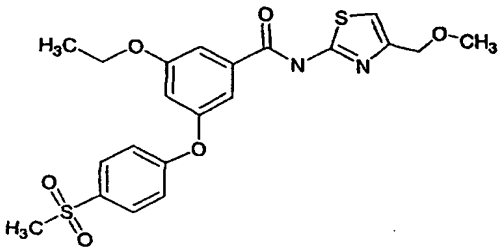
minutes. Sodium thiosulfate aqueous solution was added to the reaction liquor, the organic layer was washed with saturated aqueous sodium bicarbonate solution and then with saturated aqueous sodium chloride solution, and after drying, it was concentrated under reduced pressure, and crude product of sulfone was obtained.

To methanol solution (20 ml) of the obtained sulfone, 5 N sodium hydroxide aqueous solution 4.00 ml (20.0 mmol) was added, and the reaction liquor was stirred for one hour 30 minutes. A 5 % citric acid aqueous solution (30 ml) was added to the reaction liquid, extraction was carried out with ethyl acetate, the organic layer was washed with saturated aqueous sodium chloride solution, and after drying, it was concentrated under reduced pressure, and crude product of carboxyl body was obtained. 2-aminothiazole 1.20 g (12.0 mmol), 1-hydroxybenzotriazole hydrate 1.62 g (12.0 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride 1.53 g (8.00 mmol) were added to methylene chloride solution (40 ml) of the obtained carboxyl body, and thereafter, it was stirred at room temperature overnight. The reaction liquor was stirred for one hour 30 minutes. Water was added to the reaction liquid, extraction was carried out with ethyl acetate, the organic layer was washed with 5 % citric acid aqueous solution and then with saturated aqueous sodium chloride solution, and after drying, it was concentrated under reduced pressure, and a crude product of amide body was obtained.

4 N hydrochloric acid aqueous solution 20 ml were added to 1,4-dioxane solution (60 ml) of the obtained amide body and thereafter, were stirred at room temperature for 15 minutes. The reaction liquor was concentrated under reduced pressure, thereafter triethylamine was added, and the reaction liquor was concentrated under reduced pressure once again. The obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 1 : 2) and the title compound was obtained as a white solid. The analysis data of the compound obtained by Production Example 2 are shown below.
^{1}H-NMR ($CDCl_3$) δ : 1.33 (d, 3H, J = 6.2 Hz), 3.10 (s, 3H), 3.80 (m, 2H), 4.56 (m, 1H), 6.88 (m, 1H), 7.03 (d, 1H, J = 3.6 Hz), 7.17 (d, 2H, J = 8.8 Hz), 7.22 (m, 1H), 7.38 (m, 2H), 7.96 (d, 2H, J = 8.8 Hz), 10.8 (br, 1H).

Using the process same as in the aforesaid Production Example 1 or 2, the compounds of following Production Examples 3-58 were obtained. Below structure and analysis data of these compounds are shown.

Production Example 3



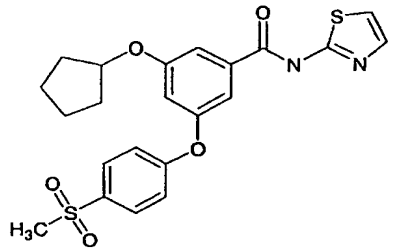
Preparation of 5-ethoxy-3-(4-methanesulphonyl phenoxy)-N-(4-methoxymethyl-thiazol-2-yl) benzamide

The compound of Production Example 3 was obtained as a colourless oily substance using the same process as in Production Example 1, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, bromoethane and 2-amino-4-methoxymethyl-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.45 (1H, t, J = 7.0 Hz), 3.10 (3H, s), 3.44 (3H, s), 4.10 (2H, q, J = 7.0 Hz), 4.45 (2H, s), 6.85 (1H, t, J = 2.0 Hz), 6.92 (1H, s), 7.14 (1H, s), 7.15 (2H, d, J = 8.8 Hz), 7.29 (1H, s), 7.94 (2H, d, J = 8.8 Hz).

ESI-MS (m/e) = 463 $(M+H)^+$

Production Example 4



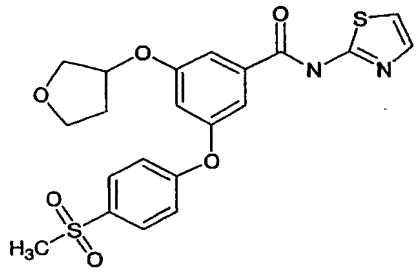
Preparation of 5-cyclopentyloxy-3-(4-methanesulphonyl phenoxy)-N-thiazol-2-yl-benzamide

The compound of preparation Production Example 4 was obtained as pale yellow oily substance using the same process as in Production Example 1, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, cyclopentyl bromide, 2-amino-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.61-1.93 (8H, m), 3.07 (3H, s), 4.75-4.79 (1H, m), 6.81 (1H, d, J = 2.0 Hz), 6.97 (1H, d, J = 3.6 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.20 (1H, s), 7.21 (1H, d, J = 3.6 Hz), 7.33 (1H, d, J = 2.0 Hz), 7.92 (2H, d, J = 8.6 Hz)

ESI-MS (m/e) = 459 $(M+H)^+$.

Production Example 5



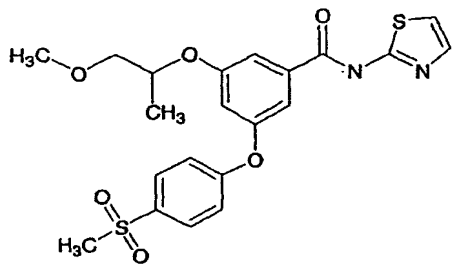
Preparation of 3-(4-methanesulphonyl phenoxy)-5-(tetrahydrofuran-3-yloxy)-N-thiazol-2-yl-benzamide

The compound of Production Example 5 was obtained as a straw-coloured oily substance using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 3-hydroxytetrahydrofuran, 2-amino-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 2.14-2.27 (2H, m), 3.08 (3H, s), 3.91-3.99 (4H, m), 4.96-4.97 (1H, m), 6.82 (1H, d, J = 1.7 Hz), 6.99 (1H, d, J = 3.6 Hz), 7.13 (2H, d, J = 8.9 Hz), 7.18 (1H, d, J = 3.6 Hz), 7.25 (1H, s), 7.30 (1H, d, J = 1.7 Hz), 7.93 (2H, d, J = 8.9 Hz)

ESI-MS (m/e) = 461 $(M+H)^+$.

Production Example 6



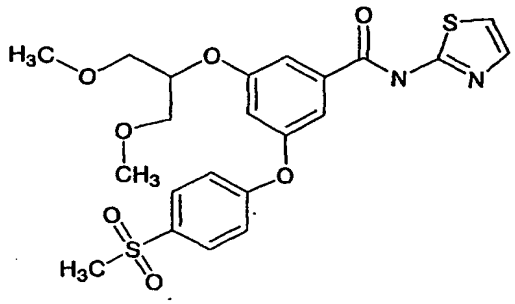
Preparation of 3-(4-methanesulphonyl phenoxy)-5-(2-methoxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide

The compound of Production Example 6 was obtained as a colourless amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-methoxy-2-hydroxy-propane and 2-amino-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.31 (d, 3H, J = 6.3 Hz), 3.07 (s, 3H), 3.38 (s, 3H), 3.55 (m, 2H), 4.59 (m, 1H), 6.89 (m, 1H), 6.98 (d, 1H, J = 3.6 Hz), 7.13 (d, 2H, J = 8.8 Hz), 7.22 (m, 1H), 7.25 (d, 1H, J = 3.6 Hz), 7.38 (m, 1H), 7.92 (d, 2H, J = 8.8 Hz).

ESI-MS (m/e) = 463 $(M+H)^+$.

Production Example 7



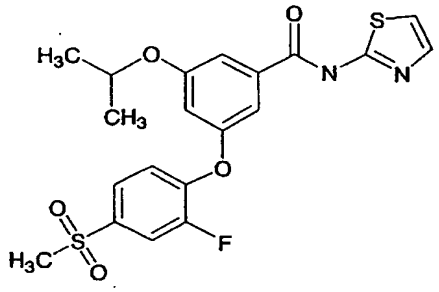
Preparation of 3-(4-methanesulphonyl phenoxy)-5-(2-methoxy-1-methoxymethyl-ethoxy)-N-thiazol-2-yl-benzamide.

The compound of Production Example 7 was obtained as a colourless amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1,3-dimethoxy-2-hydroxy-propane and 2-aminothiazole.

^{1}H-NMR ($CDCl_3$) δ = 3.08 (s, 3H), 3.39 (s, 6H), 3.63 (d, 4H, J = 4.7 Hz), 4.57 (m, 1H), 6.98 (m, 2H), 7.15 (d, 2H, J = 8.9 Hz), 7.27 (m, 2H), 7.45 (m, 1H), 7.93 (d, 2H, J = 8.9 Hz).

ESI-MS (m/e) = 493 $(M+H)^+$.

Production Example 8



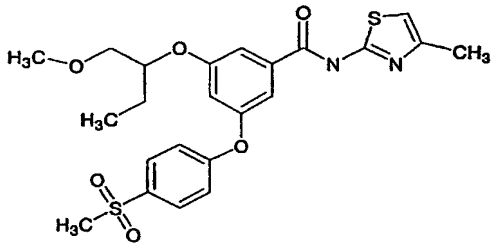
Preparation of 3-(2-fluoro-4-methanesulphonyl phenoxy)-5-isopropoxy-N-thiazol-2-yl-benzamide

The compound of Production Example 8 was obtained as pale yellow oily substance using the same process as in Production Example 1, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(2-fluoro-4-methanesulphonyl phenoxy) benzoic acid methyl ester obtained using the same process as in Production Example 1, 2-bromopropane and 2-amino-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.37 (6H, d, J = 6.1 Hz), 3.11 (3H, s), 4.60-4.64 (1H, m), 6.81 (1H, t, J = 2.2 Hz), 7.02 (1H, d, J = 3.6 Hz), 7.15 (1H, t, J = 2.2 Hz), 7.21 (1H, dd, J = 7.5, 8.5 Hz), 7.31 (1H, t, J = 2.2 Hz), 7.40 (1H, d, J = 3.6 Hz), 7.72 (1H, ddd, J = 1.2, 2.2, 7.5 Hz).

ESI-MS (m/e) = 451 $(M+H)^+$.

Production Example 9



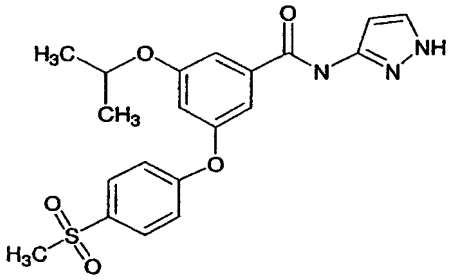
Preparation of 3-(4-methanesulphonyl phenoxy)-5-(1-methoxymethyl-propoxy)-N-(4-methyl-thiazol-2-yl)-benzamide

The compound of Production Example 9 was obtained as a white amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 2-hydroxy-1-methoxy-butane and 2-amino-4-methyl-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 0.97 (t, 3H, J = 7.3 Hz), 1.71 (quintet, 2H, J = 7.3 Hz), 2.23 (s, 3H), 3.08 (s, 3H), 3.36 (s, 3H), 3.54 (m, 2H), 4.32 (m, 1H), 6.56 (s, 1H), 6.90 (m, 1H), 7.13 (d, 2H, J = 8.9 Hz), 7.15 (m, 1H), 7.35 (m, 1H), 7.92 (d, 2H, J = 8.9 Hz), 10.6(br, 1H).

ESI-MS (m/e) = 491 $(M+H)^+$.

Production Example 10



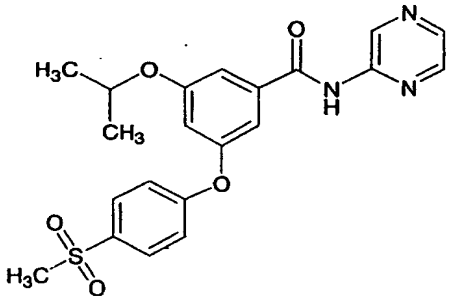
Preparation of 5-isopropoxy-3-(4-methanesulphonyl phenoxy)-N-pyrazol-3-yl-benzamide

The compound of Production Example 10 was obtained as a straw-coloured oily substance using the same process as in Production Example 1, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 2-bromopropane and 3-aminopyrazole.

^{1}H-NMR ($CDCl_3$) δ : 1.35 (d, 6H, J = 6.0 Hz), 3.06 (s, 3H), 4.58 (septet, 1H, J = 6.0 Hz), 6.00 (d, 1H, J = 3.0 Hz), 6.78 (m, 1H), 7.15 (d, 2H, J = 8.9 Hz), 7.32 (m, 1H), 7.41 (m, 1H), 7.90 (d, 2H, J = 8.9 Hz), 8.14 (d, 1H, J = 3.0 Hz).

ESI-MS (m/e) = 416 $(M+H)^+$.

Production Example 11



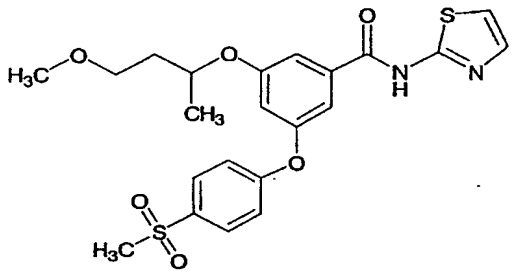
Preparation of 5-isopropoxy-3-(4-methanesulphonyl phenoxy)-N-pyrazin-2-yl-benzamide

The compound of Production Example 11 was obtained as a white amorphous material using the same process as in Production Example 1, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 2-bromopropane, 2-aminopyrazine.

^{1}H-NMR ($CDCl_3$) δ : 1.39 (d, 6H, J = 6.0 Hz), 3.09 (s, 3H), 4.62 (septet, 1H, J = 6.0 Hz), 6.82 (m, 1H), 7.14 (m, 1H), 7.17 (d, 2H, J = 8.6 Hz), 7.39 (m, 1H), 7.95 (d, 2H, 8.6 Hz), 8.30 (m, 1H), 8.41 (m, 2H), 9.68 (brs, 1H).

ESI-MS (m/e) = 428 $(M+H)^+$.

Production Example 12



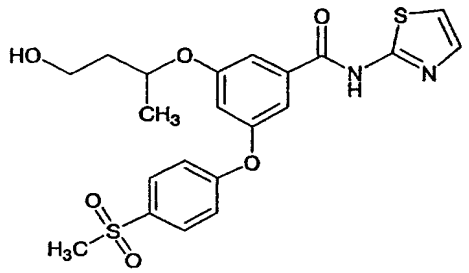
Preparation of 3-(4-methanesulphonyl phenoxy)-5-(3-methoxy-1-methyl-propoxy)-N-thiazol-2-yl-benzamide

The compound of Production Example 12 was obtained as a white amorphous material using the same process as in Production Example 1, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 2-bromo-4-methoxy butane, 2-aminothiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.34 (d, 3H, J = 6.1 Hz), 1.87(m, 1H), 2.02 (m, 1H), 3.07 (s, 3H), 3.32 (s, 3H), 3.50 (m, 2H). 4.61 (m, 1H), 6.87 (m, 1H), 6.98 (d, 1H, J = 3.4 Hz), 7.14 (d, 2H, J = 8.8 Hz), 7.21 (m, 1H), 7.25 (d, 1H, J = 3.4H poly), 7.39 (m, 1H), 7.92 (d, 2H, J = 8.8 Hz), 11.6 (br, 1H).

ESI-MS (m/e) = 477 $(M+H)^+$.

Production Example 13



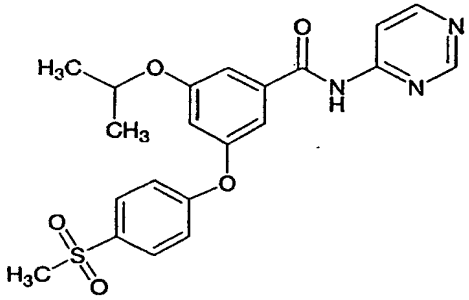
Preparation of 5-(3-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonyl phenoxy)-N-thiazol-2-yl-benzamide

The compound of Production Example 13 was obtained as a white amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert-butyldimethylsiloxy)-3-hydroxy-butane and 2-amino-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.39 (d, 3H, J = 6.1 Hz), 1.88 (m, 1H), 2.02 (m, 1H), 3.10 (s, 3H), 3.84 (m, 2H), 4.71 (m, 1H), 6.88 (m, 1H), 7.01 (d, 1H, J = 3.5 Hz), 7.17 (d, 2H, J = 8.9 Hz), 7.24 (m, 1H), 7.35 (d, 1H, J = 3.5 Hz), 7.48 (m, 1H), 7.95 (d, 2H, J = 8.9 Hz),,11.0(br, 1H).

ESI-MS (m/e) = 463 $(M+H)^+$.

Production Example 14



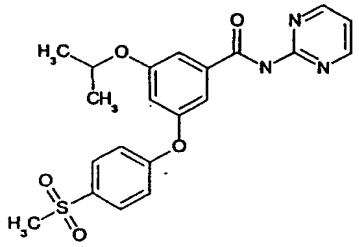
Preparation of 5-isopropoxy-3-(4-methanesulphonyl phenoxy)-N-pyrimidin-4-yl-benzamide

The compound of Production Example 14 was obtained as a white amorphous substance using the same process as in Production Example 1, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1 and 2-bromopropane and 4-amino-pyrazine.

^{1}H-NMR ($CDCl_3$) δ : 1.38 (d, 6H, J = 6.0 Hz), 3.90 (s, 3H), 4.63 (septet, 1H, J = 6.0 Hz), 6.83 (m, 1H), 7.16 (m, 1H), 7.16 (d, 2H, J = 8.9 Hz), 7.29 (m, 1H), 7.95 (d, 2H, J = 8.9 Hz), 8.31 (dd, 1H, J = 1.2, 5.6 Hz), 8.61 (m, 1H), 8.70 (d, 1H, J = 5.6 Hz), 8.90 (d, 1H, J = 1.2 Hz).

ESI-MS (m/e) = 428 $(M+H)^+$.

Production Example 15



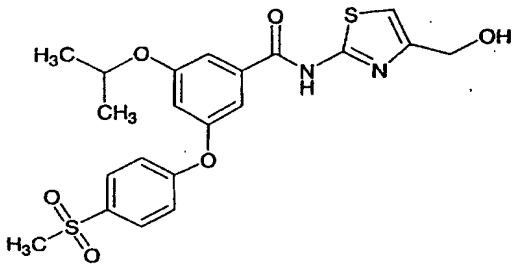
Preparation of 5-isopropoxy-3-(4-methanesulphonyl phenoxy)-N-(pyrimidin-2-yl)-benzamide

The compound of Production Example 15 was obtained as a white amorphous material using the same process as in Production Example 1, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 2-bromopropane and 2-amino-pyrazine.

^{1}H-NMR ($CDCl_3$) δ : 1.37 (d, 6H, J = 6.0 Hz), 3.08 (s, 3H), 4.62 (septet, 1H, J = 6.0 Hz), 6.79 (t, 1H, J = 2.2 Hz), 7.05-7.20 (m, 4H), 7.31 (t, 1H, J = 2.2 Hz), 7.93 (d, 2H, J = 8.8 Hz), 8.60 (m, 1H), 8.68 (d, 2H, J = 5.9 Hz).

ESI-MS (m/e) = 428 $(M+H)^+$.

Production Example 16



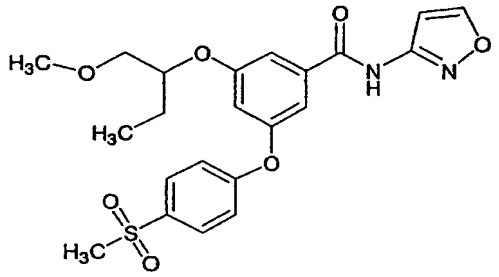
Preparation of N-(4-hydroxymethyl-thiazol-2-yl)-5-isopropoxy-3-(4-methanesulphonyl phenoxy)-benzamide

The compound of Production Example 16 was obtained as a white amorphous material using the same process as in Production Example 1, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 2-bromopropane and 2-amino-4-(tert-butyldimethylsiloxy methyl)-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.38 (6H, d, J = 6.0 Hz), 3.08 (3H, s), 4.61-4.65 (3H, m), 6.83 (1H, t, J = 2.2 Hz), 6.87 (1H, s), 7.17 (2H, d, J = 8.9 Hz), 7.18 (1H, d, J = 2.0 Hz), 7.34 (1H, d, J = 2.0 Hz), 7.95

(2H, d, J = 8.9 Hz).
ESI-MS (m/e) = 463 $(M+H)^+$.

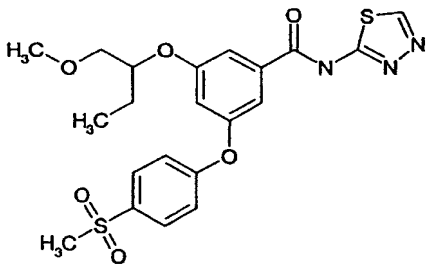
Production Example 17



Preparation of N-(isoxazol-3-yl)-3-(4-methanesulphonyl phenoxy)-5-(1-methoxymethyl-propoxy)-benzamide

The compound of Production Example 17 was obtained as a colourless oily substance using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 2-hydroxy-1-methoxy-butane and 3-amino-oxazole.
^{1}H-NMR ($CDCl_3$) δ : 0.99 (t, 3H, J = 7.5 Hz), 1.74 (quintet, 2H, J = 7.5 Hz), 3.01 (s, 3H), 3.38 (s, 3H), 3.57 (m, 2H), 4.39 (m, 1H), 6.89 (m, 1H), 7.16-7.12 (m, 2H), 7.14 (d, 2H, J = 8.8 Hz), 7.32 (m, 1H), 7.93 (d, 2H, J = 8.8 Hz), 8.33 (s, 1H, J = 1.9 Hz), 8.64 (m, 1H).
ESI-MS (m/e) = 461 $(M+H)^+$.

Production Example 18

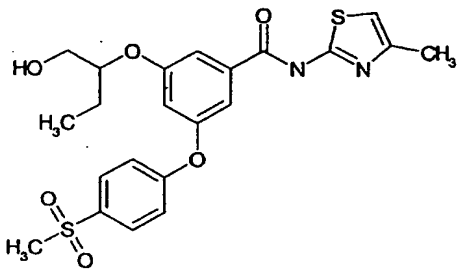


Preparation of 3-(4-methanesulphonyl phenoxy)-5-(1-methoxymethyl-propoxy)-N-[1,3,4] thiadiazol-2-yl-benzamide

The compound of Production Example 18 was obtained as disapproval oily substance using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 2-hydroxy-1-methoxy-butane and 2-amino-1,3,4-thiadiazole.

^{1}H-NMR ($CDCl_3$) δ : 0.98 (t, 3H, J = 7.5 Hz), 1.75 (quintet, 2H, J = 7.5 Hz), 3.07 (s, 3H), 3.37 (s, 3H), 3.56 (m, 2H), 4.45 (m, 1H), 6.93 (m, 1H), 7.14 (d, 2H, J = 8.9 Hz), 7.44 (m, 1H), 7.53 (m, 1H), 7.91 (d, 2H, J = 8.9 Hz), 8.73 (s, 1H), 12.0 (br, 1H).
ESI-MS (m/e) = 478 $(M+H)^+$.

Production Example 19

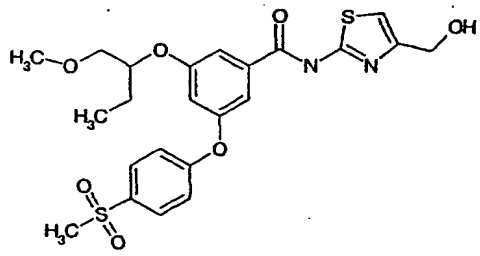


Preparation of 5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonyl phenoxy)-N-(4-methyl-thiazol-2-yl)-benzamide

The compound of Production Example 19 was obtained as a colourless amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert-butyldimethylsiloxy)-2-hydroxy-butane and 2-amino-4-methyl-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 0.99 (t, 3H, J = 7.3 Hz), 1.68 (m, 2H), 2.28 (d, 3H, J = 1.0 Hz), 3.09 (s, 3H), 3.82 (m, 2H), 4.36 (m, 1H), 6.57 (d, 1H, J = 1.0 Hz), 6.75 (m, 1H), 7.11 (m, 1H), 7.13 (d, 2H, J = 8.9 Hz), 7.28 (m, 1H), 7.93 (d, 2H, J = 8.9 Hz), 10.8(br, 1H).
ESI-MS (m/e) = 477 $(M+H)^+$.

Production Example 20



Preparation of N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonyl phenoxy)-5-(1-methoxymethyl-propoxy)-benzamide.

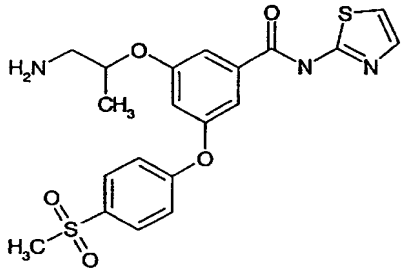
The compound of Production Example 20 was obtained as a white amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl

ester obtained by Production Example 1, 2-hydroxy-1-methoxy-butane and 2-amino-4-(tert-butyl dimethyl siloxy methyl)-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.01 (t, 8H, J = 7.5 Hz), 1-76 (quintet, 2H, J = 7.5 Hz), 3.10 (s, 3H), 3.40 (s, 3H), 3.59 (m, 2H), 4.43 (m, 1H), 4.64 (s, 2H), 6.89 (s, 1H), 6.94 (m, 1H), 7.18 (d, 2H, J = 9.0 Hz), 7.20 (m, 1H), 7.40 (m, 1H), 7.96 (d, 2H, J = 9.0 Hz), 10.0 (br, 1H).

ESI-MS (m/e) = 507 $(M+H)^+$.

Production Example 21



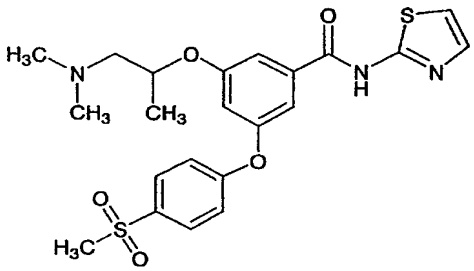
Preparation of 5-(2-amino-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-thiazol-2-yl-benzamide

The compound of Production Example 21 was obtained as a white amorphous substance using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert butoxycarbonyl amino)-2-hydroxy-propane and 2-aminothiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.30 (d, 3H, J = 6.0 Hz), 2.92 (d, 2H, J = 6.0 Hz), 3.09 (s, 3H), 4.41 (sextet, 1H, J = 6.0 Hz), 6.86 (m, 1H), 6.98 (d, 1H, J = 3.5 Hz), 7.14 (d, 2H, J = 8.9 Hz), 7.21 (d, 1H, J = 3.5 Hz), 7.25 (m, 1H), 7.42 (m, 1H)8.87 (d, 2H, J = 8.9 Hz).

ESI-MS (m/e) = 448 $(M+H)^+$.

Production Example 22



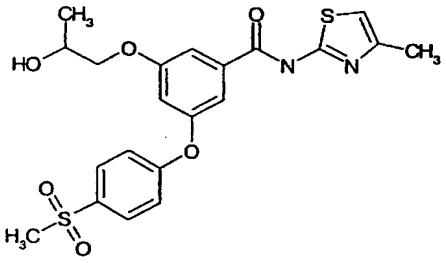
Preparation of 5-(2-dimethylamino-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-thiazol-2-yl-benzamide

The compound of Production Example 22 was obtained as a straw-coloured oily substance using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-dimethylamino-2-hydroxypropane and 2-amino-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.28 (d, 3H, J = 6.2 Hz), 2.30 (s, 6H), 2.42 (dd, 1H, J = 4.4, 13.0 Hz), 2.68 (dd, 1H, J = 6.2Hz, 13.0 Hz), 3.09 (s, 3H), 4.56 (dt, 1H, J = 4.5, 6.2 Hz), 6.89 (m, 1H), 7.00 (d, 1H, J = 3.6 Hz), 7.15 (d, 2H, J = 8.9 Hz), 7.22 (m, 1H), 7.28 (d, 1H, 3.6 Hz), 7.41 (m, 1H), 7.93 (d, 2H, J = 8.9 Hz), 11.4(br, 1H).

ESI-MS (m/Le) = 476 $(M+H)^+$.

Production Example 23



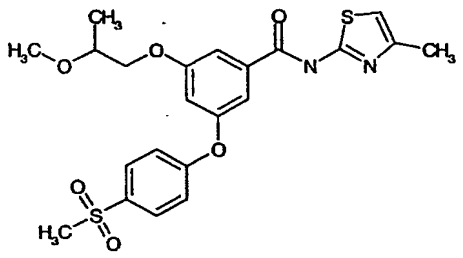
Preparation of 5-(2-hydroxy-propoxy)-3-(4-methanesulphonyl phenoxy)-N-(4-methyl-thiazol-2-yl)-benzamide

The compound of Production Example 23 was obtained as a white amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 2-(tert-butyldimethylsiloxy)-1-hydroxy-propane and 2-amino-4-methylthiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.28 (d, 3H, J = 6.4 Hz), 2.20 (d, 3H, J = 1.0 Hz), 3.08 (s, 3H), 3.79 (m, 1H), 3.93 (m, 1H), 4.20 (m, 1H), 6.57 (d, 1H, J = 1.0 Hz), 6.78 (m, 1H), 7.09 (d, 2H, J = 8.9 Hz), 7.16 (m, 1H), 7.25 (m, 1H), 7.92 (d, 2H, J = 8.9 Hz), 11.2 (br, 1H).

ESI-MS (m/e) = 463 $(M+H)^+$.

Production Example 24



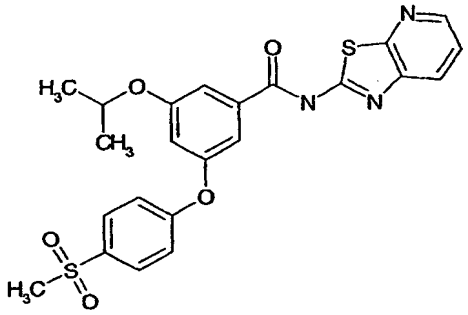
Preparation of 3-(4-methanesulphonyl phenoxy)-5-(2-methoxy-propoxy)-N-(4-methyl-thiazol-2-yl)-benzamide

The compound of Production Example 24 was obtained as a colourless oily substance using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1 and 1-hydroxy-2-methoxy-propane and 2-amino-4-methylthiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.26 (d, 3H, J = 6.3 Hz), 2,22 (d, 3H, J = 1.1 Hz), 3,08 (s, 3H), 3.43 (s, 3H), 3.72 (m, 1H), 3.93 (m, 2H), 6.57 (d, 1H, J = 1.1 Hz), 6.86 (m, 1H), 7.12 (d, 2H, J = 8.6 Hz), 7.16 (m, 1H), 7.29 (m, 1H), 7.92 (d, 2H, J = 8.6 Hz), 10.6 (br, 1H).

ESI-MS (m/e) = 477 $(M+H)^+$.

Production Example 25



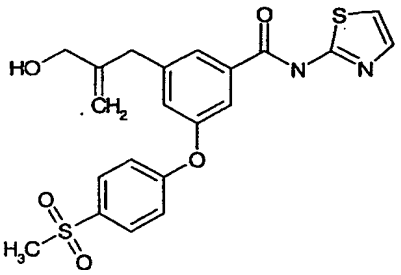
Preparation of 5-isopropoxy-3-(4-methanesulphonyl phenoxy)-N-(thiazolo [5,4-b] pyridin-2-yl)-benzamide

The compound of Production Example 25 was obtained as a straw-coloured solid using the same process as in Production Example 1, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 2-bromopropane and 2-amino-thiazolo [5,4-b] pyridine.

^{1}H-NMR ($CDCl_3$) δ : 1.37 (6H, d, J = 6.0 Hz), 3.09 (3H, s), 4.59-4.63 (1H, m), 6.84 (1H, t, J = 1.8 Hz), 7.14 (2H, d, J = 8.9 Hz), 7.19 (1H, t, J = 1.8 Hz), 7.34 (1H, t, J = 1.8 Hz), 7.38 (1H, dd, J = 4.7, 8.1 Hz), 7.92 (1H, dd, J = 1.5, 8.1 Hz), 7.94 (2H, d, J = 8.9 Hz), 8.53 (1H, dd, J= 1.5, 4.7 Hz).

ESI-MS (m/e). 484 $(M+H)^+$.

Production Example 26

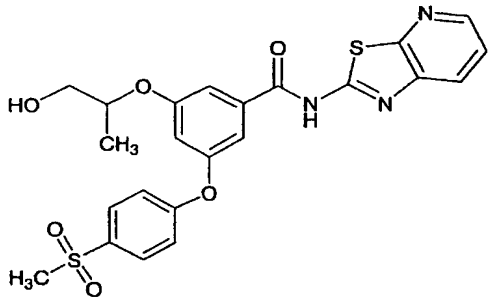


Preparation of 5-(2-hydroxymethyl-allyl)-3-(4-methanesulphonyl phenoxy)-N-thiazol-2-yl-benzamide.

^{1}H-NMR ($CDCl_3$) δ : 3.08 (3H, s), 3.49 (2H, s), 4.06 (2H, s), 4.91 (1H, s), 5.19 (1H, s), 7.00 (1H, d, J = 3.3 Hz), 7.11 (2H, d, J = 9.0 Hz), 7.13 (1H, d, J = 3.3 Hz), 7.20 (1H, s), 7.55 (1H, s), 7.67 (1H, s), 7.92 (2H, d, J = 9.0 Hz).

ESI-MS (m/e) = 445 $(M+H)^+$

Production Example 27



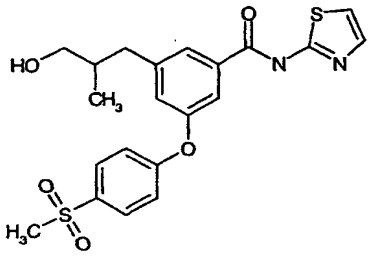
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-thiazolo [5,4-b] pyridin-2-yl-benzamide.

The compound of Production Example 27 was obtained as a straw-coloured solid using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 2-amino-thiazolo [5,4-b] pyridine.

^{1}H-NMR ($CDCl_3$) δ : 1.34 (6H, d, J = 6.2 Hz), 3.11 (3H, s), 3.74 (2H, d, J = 4.6 Hz), 4.57-4.62 (1H, m), 6.92 (1H, t, J = 1.8 Hz) 7.19 (2H, d, J = 8.9 Hz), 7.36 (1H, t, J = 1.8 Hz), 7.43 (1H, dd, JF4.7, 8.2 Hz), 7.49 (1H, t, J = 1.8 Hz), 7.94 (2H, d, J = 8.9 Hz), 8.03 (1H, dd, J = 1.4, 8.2 Hz), 8.49 (1H, dd, J = 1.4, 4.7 Hz).

ESI-MS (m/e) = 484 $(M+H)^+$.

Production Example 28

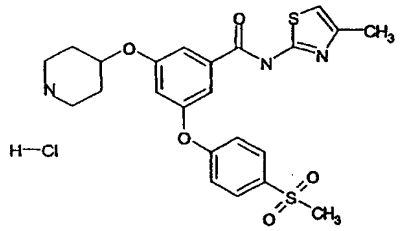


Preparation of 5-(3-hydroxy-2-methyl-propyl)-3-(4-methanesulphonyl phenoxy)-N-thiazol-2-yl-benzamide.

^{1}H-NMR ($CDCl_3$) δ : 0.94 (6H, d, J = 6.7 Hz), 1.97-2.05 (1H, m), 2.50-2.94 (2H, m), 3.08 (3H, s), 3.50-3.56 (2H, m), 7.03 (1H, d, J = 3.5 Hz), 7.13 (2H, d, J = 8.8 Hz), 7.17 (1H, s), 7.42 (1H, d, J = 3.5 Hz), 7.52 (1H, s), 7.63 (1H, s), 7.93 (2H, d, J = 8.8 Hz).

ESI-MS (m/e) = 447 $(M+H)^+$.

Production Example 29

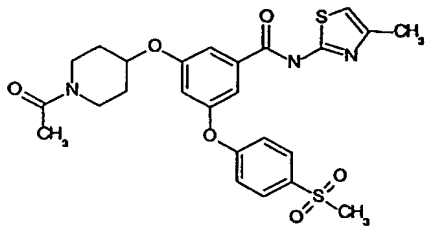


Preparation of 3-(4-methanesulphonyl phenoxy)-N-(4-methyl-thiazol-2-yl)-5-(piperidin-4-yl-oxy)-benzamide hydrochloride

The compound of Production Example 29 was obtained as white crystal using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert butoxycarbonyl)-4-hydroxy-piperidine and 2-amino-4-methyl-thiazole.

^{1}H-NMR (CD_3OD) δ = 1.93 (m, 2H), 2.11 (m, 2H), 2.31 (s, 3H), 2.99 (s, 3H), 3.13 (m, 2H), 3.30 (m, 2H), 4.75 (m, 1H), 6.89 (s, 1H), 7.11 (m, 2H, J = 8.9 Hz), 7.27 (m, 1H), 7.52 (m, 1H), 7.84 (d, 2H, J = 8.9 Hz).

Production Example 30



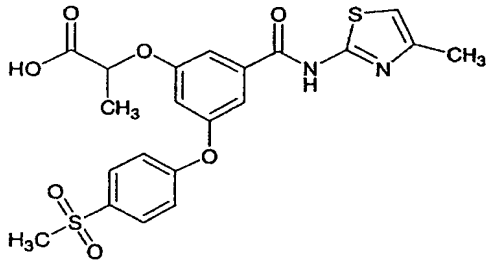
Preparation of 5-(1-acetyl-piperidin-4-yloxy)-3-(4-methanesulphonyl phenoxy)-N-(4-methyl-thiazol-2-yl)-benzamide

The compound of Production Example 30 was obtained as a white amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-acetyl-4-hydroxy-piperidine and 2-amino-4-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.80 (m, 3H), 2.20-2.00 (m, 2H), 2.14 (s, 3H), 2.51 (s, 3H), 3.10 (s, 3H), 3.50 (m, 1H), 3.75 (m, 1H), 4.01 (m, 1H), 4.84 (m, 1H), 4.84(m, 1H), 6.71 (s, 1H), 6.92 (m, 1H), 7.18 (d, 2H, J = 8.9 Hz), 7.43 (m, 1H), 7.76 (m, 1H), 7.96 (d, 2H, J = 8.9 Hz).

ESI-MS (m/e) = 530 $(M+H)^+$.

Production Example 31



Preparation of 2-[3-(4-methanesulphonyl phenoxy)-5-(4-methyl-thiazol-2-yl-carbamoyl)-phenoxy] propionic acid

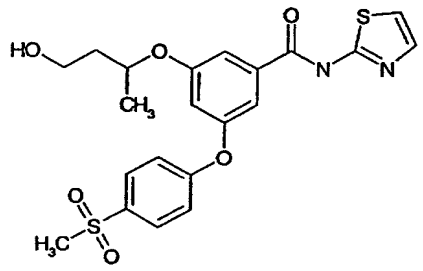
The compound of Production Example 31 was obtained as white crystal using the same process as in Production Example 1, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 2-bromopropionic acid tert-butyl ester and 2-amino-4-methyl-thiazole. Moreover, during production of this compound, the removal of tert-butyl group which is a protecting group of carboxyl group can be carried out by the process in accordance with literature (for example Protective Groups in Organic Synthesis, T. W. Green, 2nd Edition, John Wiley & Sons Co., 1991, or the like), a method in accordance with it or combination of these and conventional methoda.

^{1}H-NMR (DMSO-d_6) δ : 1.53 (d, 3H, J = 6.8 Hz), 2.28 (s, 3H), 3.27 (s, 3H), 5.03 (septet, 1H, J =

6.8 Hz), 6.82 (m, 1H), 6.94 (m, 1H), 7.25 (d, 2H, J = 8.8 Hz), 7.42 (m, 1H), 7.50 (m, 1H), 7.95 (d, 2H, J = 8.8 Hz.

ESI-MS (m/e) = 477 $(M+H)^+$.

Production Example 32



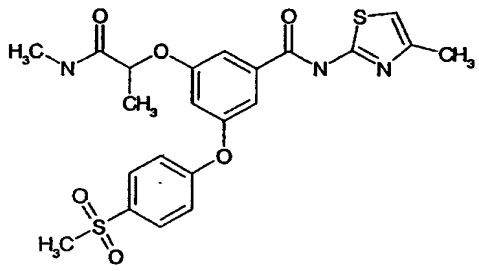
Preparation of 5-(3-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonyl phenoxy)-N-thiazol-2-yl-benzamide

The compound of Production Example 32 was obtained as white amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert-butyldimethylsiloxy-3-hydroxy butane and 2-aminothiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.35 (d, 3H, J = 6.0 Hz), 1.83 (m, 1H), 2.00 (m, 1H), 3.08 (s, 3H), 3.78 (m, 2H), 4.65 (m, 1H), 6.86 (m, 1H), 6.98. (m, 1H, J = 3.5 Hz) 7.13 (d, 2H, J = 8.8 Hz), 7.21 (d, 1H, J = 3.5 Hz), 7.23 (m, 1H), 7.45 (m, 1H), 7.91 (d, 2H, J = 8.8 Hz), 12.1 (br, 1H).

ESI-MS (m/e) = 463 $(M+H)^+$.

Production Example 33

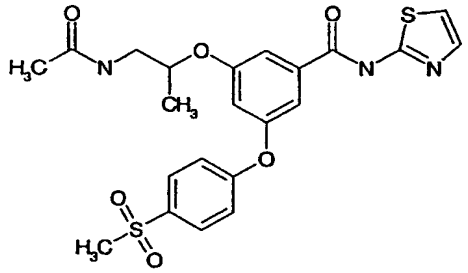


Preparation of 3-(4-methanesulphonyl phenoxy)-5-(1-methylcarbamoyl-ethoxy)-N-(4-methyl-thiazol-2-yl)-benzamide

The compound of Production Example 33 was obtained as a white amorphous material by reacting 2-[3-(4-methanesulphonyl phenoxy)-5-(4-methyl-thiazol-2-yl-carbamoyl)-phenoxy] propionic acid obtained by Production Example 31 and methylamine. The reaction of the said compound and

methylamine obtained by Production Example 31 is amide bond forming reaction, and can be carried out by the process of literature (for example, Basis and Experiment of peptide synthesis, Nobuo IZUMIYA, Maruzen, 1983, Comprehensive Organic Synthesis, vol 6., Pergamon Press Co., 1991 or the like), method in accordance with it or combination of these and conventional methods.
^{1}H-NMR ($CDCl_3$) δ : 1.59 (s, 3H), 2.26 (s, 3H), 2.86 (d, 3H, J = 4.7 Hz), 3.10 (s, 3H), 4.73 (q, 1H, J = 6.6 Hz), 6.47 (m, 1H), 6.57 (m, 1H), 6.83 (m, 1H), 7.12 (d, 2H, J = 8.8 Hz), 7.22 (m, 1H), 7.31 (m, 1H), 7.93 (d, 2H, J = 8.8 Hz), 11.0(br, 1H).
ESI-MS (m/e) = 490 $(M+H)^+$.

Production Example 34



Preparation of 5-(2-acetylamino-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-thiazol-2-yl-benzamide

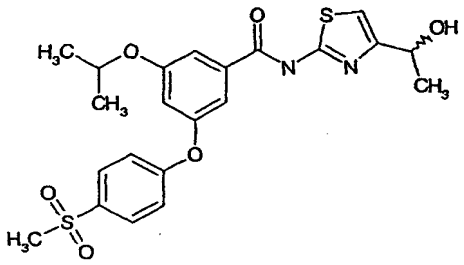
The compound of Production Example 34 was obtained as a white amorphous material by reacting acetic acid and 5-(2-amino-1-methyl-ethoxy)-3-(4-methanesulphonyl-phenoxy)-N-thiazol-2-yl-benzamide which was obtained by converting, to amino group, the hydroxy group of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl-phenoxy)-N-thiazol-2-yl-benzamide obtained by Production Example 2.

The conversion reaction from hydroxy group to amino group can be carried out by converting the hydroxy group to mesyl group, thereafter reacting said mesyl bvody and sodium azide to form an azide body, thereafter, by reducing the azido group by using the like of triphenyl phosphine and the like. Said transformation can be carried out by the process of literature (Comprehensive Organic Transformations, by Richard C. Larock, the second edition, John Wiley & Sons Co, 1999), method in accordance with it or combination of these and conventional methods.

Moreover, the reaction of acetic acid and 3-(2-amino-1-methyl-ethoxy)-5-(4-methanesulphonyl-phenoxy)-N-thiazol-2-yl-benzamide is amide bond forming reaction, and it can be carried out by the same method as in amide bond forming reaction used in step 1 and other steps, a method in accordance with it or combination of these and conventional methods.
^{1}H-NMR ($CDCl_3$) δ : 1.33 (d, 3H, J = 6.0 Hz), 2.03 (s, 3H), 3.10-(s, 3H), 3.49 (t'2H, J = 5.8 Hz),

4.56 (sextet, 1H, J = 6.0 Hz), 5.98 (t, 1H, J = 5.8 Hz), 6.87 (m, 1H), 7.00 (d, 1H, J = 3.6 Hz), 7.15 (d, 2H, J = 8.7 Hz), 7.28 (m, 2H), 7.54 (m, 1H), 7.94 (d, 2H, J = 8.7 Hz), 11.9(br, 1H).
ESI-MS (m/e) = 490 $(M+H)^+$.

Production Example 35

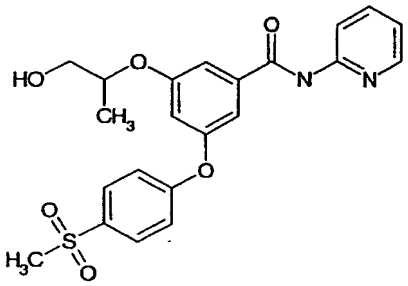


Preparation of N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-5-isopropoxy-3-(4-methanesulphonyl phenoxy)-benzamide

The compound of Production Example 35 was obtained as white solid using the same process as in Production Example 1, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 2-bromopropane and 2-amino-4-(1-tert-butyldimethylsiloxy-ethyl)-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.38 (6H, d, J = 6.0 Hz), 1.55-1.60 (3H, br), 3.08 (3H, s), 4.63 (1H, quint, J = 6.0 Hz), 4.90 (1H, q, J = 6.6 Hz), 6.t79-6.85 (2H, m), 7.16 (2H, d, J = 8.8 Hz), 7.20 (1H, br), 7.36 (1H, br), 7.94 (2H, d, J = 8.8 Hz).
ESI-MS (m/e) = 477 $(M+H)^+$.

Production Example 36



Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-pyridin-2-yl-benzamide

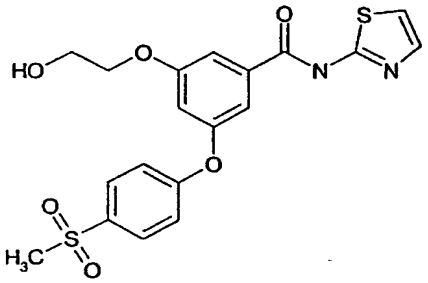
The compound of Production Example 36 was obtained as white crystal using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 2-

aminopyridine.

^{1}H-NMR ($CDCl_3$) δ : 1.32 (3H, d, J = 3.2 Hz), 3.08 (3H, s), 3.76-3.79 (2H, m), 4.57-4.63 (1H, m), 6.48 (1H, t, J = 2.0 Hz), 7.13-7.17 (1H, m), 7.15 (2H, d, J = 8.8 Hz), 7.18 (1H, d, J = 2.0 Hz), 7.35 (1H, d, J = 2.0 Hz), 7.76 (1H, ddd, J = 1, 6,5.1, 8.4 Hz), 7.93 (2H, d, J = 8.8 Hz), 8.30 (1H, d, J = 5.1 Hz), 8.34 (1H, d, J = 8.4 Hz).

ESI-MS (m/e) = 443 $(M+H)^+$.

Production Example 37



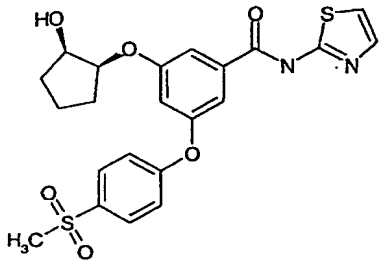
Preparation of 5-(2-hydroxy-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-thiazol-2-yl-benzamide

The compound of Production Example 37 was obtained as a white amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert dimethyl butyl siloxy)-2-hydroxy ethane and 2-aminothiazole.

^{1}H-NMR ($CDCl_3$) δ : 3.10 (s, 3H), 4.01 (t, 2H, J = 4.5Hg), 4.14 (t, 2H, J = 4.5H balance), 6.87 (m, 1H), 7.02 (d, 1H, J = 3.0 Hz), 7.16 (d, 2H, J = 8.4 Hz), 7.30 (m, 2H), 7.38 (m, 1H), 7.95 (d, 2H, J = 8.4 Hz), 11.3(br, 1H).

ESI-MS (m/e) = 435 $(M+H)^+$

Production Example 38



Preparation of 5-(2-hydroxy-cyclopentyl oxy)-3-(4-methanesulphonyl phenoxy)-N-thiazol-2-yl-benzamide

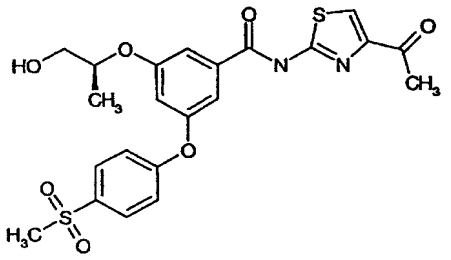
The compound of Production Example 38 was obtained as a straw-coloured oily substance using

the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert-butyl diphenyl siloxy)-2-hydroxy cyclopentane and 2-aminothiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.62-2.08 (6H, m), 3.08 (3H, s), 4.24-4.30 (1H, m), 4.55-4.60 (1H, m), 6.87 (1H, t, J = 2.0 Hz), 7.00 (1H, d, J = 3.6 Hz), 7.14 (2H, d, J = 8.8 Hz), 7/25 (1H, t, J = 2.0 Hz), 7.25 (1H, d, J = 3.6 Hz), 7.40 (1H, t, J = 2.0 Hz), 7.93 (2H, d, J = 8.8 Hz).

ESI-MS (m/e) = 475 $(M+H)^+$.

Production Example 39

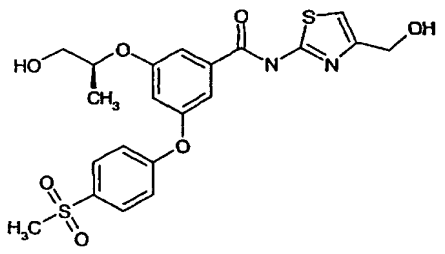


Preparation of N-(4-acetyl-thiazol-2-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-benzamide

The compound of Production Example 39 was obtained as a white amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 4-acetyl-2-amino-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.32 (3H, d, J = 6.2 Hz), 2.58 (3H, s), 3.10 (3H, s), 3.80 (2H, d, J = 5.2 Hz), 4.63 (1H, q, J = 5.6 Hz), 6.81-6.89 (1H, m), 7.12-7.19 (3H, m), 7.38 (1H, br), 7.83 (1H, d, J = 2.0 Hz), 7.95 (2H, dd, J = 8.9 Hz) ESI-MS (m/e) = 491 $(M+H)^+$

Production Example 40



Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonyl phenoxy)-benzamide

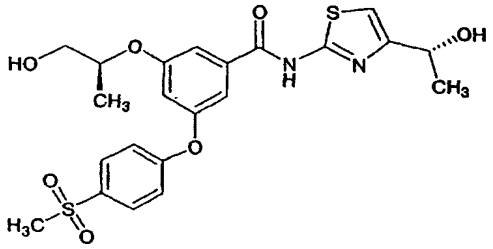
The compound of Production Example 40 was obtained as white solid using the same process as in

Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 2-amino-4-tert-butyldimethylsiloxy methylthiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.31 (3H, d, J = 6.2 Hz), 3.09(3H, s), 3.75-3.80 (2H, m), 4.55-4.66 (3H, m), 6.83-6.86 (1H, m), 6.88 (1H, s), 7.12-7.20 (3H, m), 7.33-7.36 (1H, m), 7.94 (2H, d, J = 8.6 Hz).

ESI-MS (m/e) = 479 $(M+H)^+$.

Production Example 41



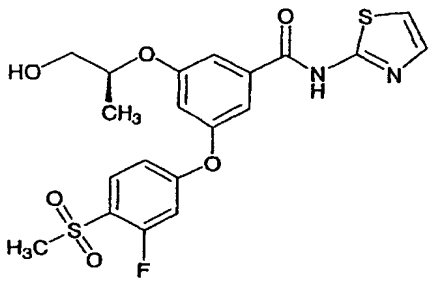
Preparation of N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-benzamide

The compound of Production Example 41 was obtained as a straw-coloured oily substance using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 2-amino-4-(1-tert-butyldimethylsiloxy-ethyl) thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.31 (3H, d, J = 6.2 Hz), 1.49 (3H, d, J = 6.5 Hz), 3.12 (3H, s), 3.68 (2H, d, J = 5.0 Hz), 4.60 (1H, q, J = 6.2 Hz), 4.80-4.90 (1H, m), 6.94 (1H, s), 6.96-6.99 (1H, m), 7.23 (2H, d, J = 8.9 Hz), 7.29-7.32 (1H, m), 7.47-7.50 (1H, m), 7.89 (1H, s), 7.96 (2H, d, J = 8.9 Hz).

ESI-MS (m/e) = 493 $(M+H)^+$.

Production Example 42



Preparation of 3-(3-fluoro-4-methanesulphonyl phenoxy)-5-(2-hydroxo-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide

1-bromo-2-fluoro-4-iodobenzene 20.4 g (0.68 mol), cesium carbonate 20.8(0.68 mol) and copper (II) cyanide 20.8g (0.64 mol) were added to pyridine solution (50.0 ml) of 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester 9.00 g (0.43 mol) and thereafter, under a nitrogen atmosphere, were stirred at 130°C for eight hours. The reaction liquor was filtered, and thereafter concentrated under reduced pressure, and ethyl acetate and saturated ammonium chloride aqueous solution were added to the obtained residue, and the organic layer was washed with saturated aqueous sodium chloride solution, and after drying, it was concentrated under reduced pressure. The obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 9 : 1) and 3-(4-bromo-3-fluoro-phenoxy)-5-methoxymmethoxy benzoic acid methyl ester 10.6 g (yield = 65%) were obtained as a yellow oily substance.

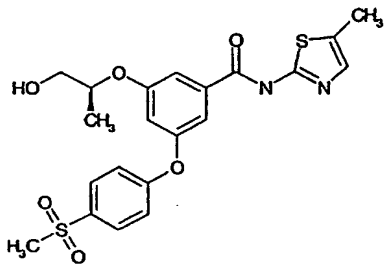
Methane sulphinic acid sodium 757 mg (7.41 mmol) and copper iodide 1.41 g (7.41 mmol) were added to dimethylsulfoxide solution (6.0 ml) of the obtained ester 357 mg (0.93 mmol), and thereafter the reaction liquor was stirred at 120°C for six hours. Sodium chloride water-ammonia water (9 : 1) was added to the reaction liquid, extraction was carried out with ethyl acetate, it was washed with saturated aqueous sodium chloride solution, and after drying, the organic layer was concentrated under reduced pressure. The obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 2 : 1) and 3-(3-fluoro-4-methanesulphonyl-phenoxy)-5-methoxymethoxy benzoic acid methyl ester 170 mg (yield = 48%) were obtained as a colourless oily substance.

To methylene chloride solution (60.0 ml) of the obtained ester 3.34 g (8.69 mmol), trifluoroacetic acid 30.0 ml were added, and the reaction liquor was stirred at room temperature for two hours. The reaction liquor was concentrated under reduced pressure and the obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 3 : 7) and 3-(3-fluoro-4-methanesulphonyl-phenoxy)-5-hydroxybenzoic acid methyl ester 2.59 g (yield = 88%) were obtained as a colourless oily substance.

(2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane 87.0 mg (0.46 mmol) and triphenyl phosphine 119 mg (0.46 mmol) were added to tetrahydrofuran solution (1.0 ml) of the obtained phenol body 77.5 mg (0.23 mmol), and thereafter, 40 % toluene solution 0.25 ml (0.57 mmol) of diethylazo dicarboxylate was added, and the mixture was stirred at room temperature overnight. The reaction liquor was concentrated under reduced pressure and the obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 2 : 1) and 5-((1S)-2-(t-butyldimethylsiloxy)-1-methyl-ethoxy)-3-(3-fluoro-4-methanesulphonyl-phenoxy)-benzoic acid methyl ester 80.0 mg (yield = 69%) were obtained as a colourless oily substance.

The compound of Production Example 42 was obtained as a colourless oily substance using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using the obtained 5-((1S)-2-(t-butyldimethylsiloxy)-1-methyl-ethoxy)-3-(3-fluoro-4-methanesulphonyl-phenoxy)-benzoic acid methyl ester and 2-amino-thiazole.
^{1}H-NMR ($CDCl_3$) δ : 1.32 (3H, d, J = 6.3 Hz), 3.23 (3H, s), 3.78-3.80 (2H, m), 4.56-4.61 (1H, m), 6.83-6.94 (3H, m), 7.01 (1H, d, J = 3.5 Hz), 7.23 (1H, t, J = 1.8 Hz), 7.37 (1H, d, J = 3.5 Hz), 7.41 (1H, t, J = 1.8 Hz), 7.94 (1H, t, J = 8.2 Hz).
ESI-MS (m/e) = 467 $(M+H)^+$

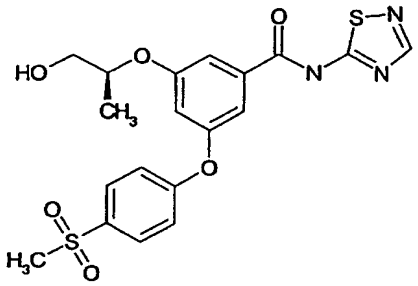
Production Example 43



Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-(5-methyl-thiazol-2-yl) benzamide

The compound of Production Example 43 was obtained as a straw-coloured oily substance using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 2-amino-5-methylthiazole.
^{1}H-NMR ($CDCl_3$) δ : 1.29 (3H, d, J = 6.2 Hz), 2.37 (3H, s), 3.08 (2H, s), 3.69-3.76 (2H, m), 4.52-4.57 (1H, m), 6.82 (1H, t, J = 2.0 Hz), 6.88 (1H, s), 7.12 (2H, d, J = 8.8 Hz), 7.20 (1H, d, J = 2.0 Hz), 7.35 (1H, d, J = 2.0 Hz), 7.92 (2H, d, J = 8.8 Hz).
ESI-MS (m/e) = 463 $(M+H)^+$

Production Example 44



Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-([1,2,4]

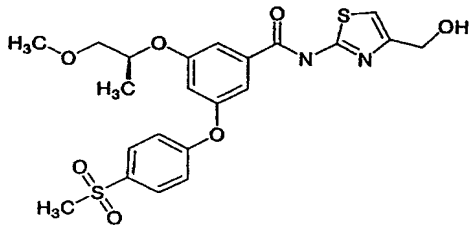
thiadiazol-5-yl)-benzamide

The compound of Production Example 44 was obtained as a straw-coloured oily substance using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 5-amino-1,2,4-thiadiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.30 (3H, d, J = 6.2 Hz), 3.12 (3H, s), 3.68 (2H, d, J = 5.1 Hz), 4.58-4.85 (1H, m), 7.00 (1H, s), 7.23 (2H, d, J = 8.9Hg), 7.37 (1H, s), 7.56 (1H, s), 7.95 (2H, d, J = 8.9 Hz), 8.37 (1H, s).

ESI-MS (m/e) = 450 $(M+H)^+$

Production Example 45



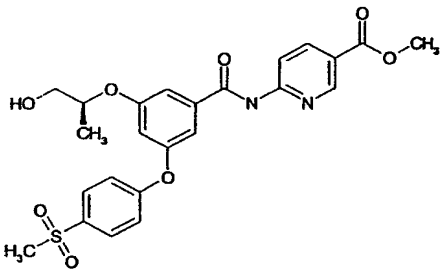
Preparation of N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonyl phenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide

The compound of Production Example 45 was obtained as a colourless amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 2-hydroxy-1-methoxy propane and 2-amino-4-tert-butyldimethylsiloxy methylthiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.35 (3H, d, J = 6.3 Hz), 3.09 (3H, s), 3.41 (3H, s), 3.49-3.64 (2H, m), 4.58-4.67 (3H, m), 6.87-6.92 (2H, m), 7.13-7.20 (3H, m), 7.35-7.38 (1H, br), 7.94 (2H, d, J = 8.8 Hz).

ESI-MS (m/e) = 493 $(M+H)^+$

Production Example 46



Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-(5-

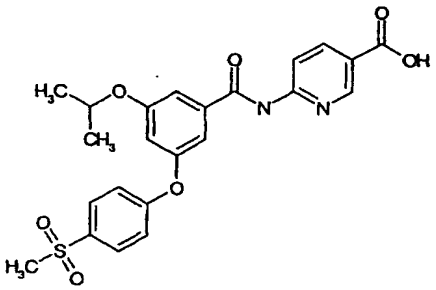
methoxycarbonyl-pyridin-2-yl)-benzamide

The compound of Production Example 46 was obtained as a white amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 2-amino-5-methoxycarbonyl-pyridine.

^{1}H-NMR ($CDCl_3$) δ : 1.34 (d, 3H, J = 6.0 Hz), 3.10 (s, 3H), 3.80 (m, 2H), 3.96 (s, 3H), 4.61 (m, 1H), 6.80 (m, 1H), 7.16 (d, 2H, J = 8.8 Hz), 7.20 (m, 1H), 7.37 (m, 1H), 7.94 (d, 2H, J = 8.8 Hz), 8.33-8.46 (m, 2H), 8.80 (br, 1H), 8.93 (m, 1H).

ESI/MS(m/e) = 501 $(M+H)^+$

Production Example 47



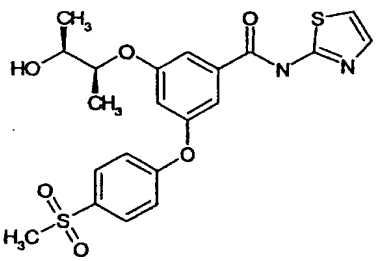
Preparation of 6-[5-isopropoxy-3-(4-methanesulphonyl phenoxy)-benzoylamino] nicotinic acid

The compound of Production Example 47 is obtained as white solid using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 6-amino-nicotinic acid.

^{1}H-NMR(DMSO-d_6) δ = 1.29 (d, 6H, J = 6.0 Hz), 3.20 (s, 3H), 4.76 (septet, 1H, J = 6.0 Hz), 6.94 (m, 1H), 7.23 (d, 2H, J = 8.8 Hz), 7.33 (m, 1H)) 7.49 (m, 1H), 7.94 (d, 2H, J = 8.8 Hz), 8.29 (m, 2H), 8.87 (m, 1H), 11.2 (s, 1H)

ESI-MS (m/e) = 471 $(M+H)^+$.

Production Example 48



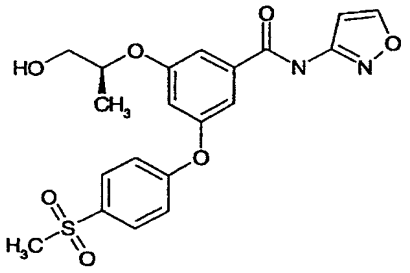
Preparation of 5-(2-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonyl phenoxy)-N-thiazol-2-yl-benzamide

The compound of Production Example 48 was obtained as pale yellow oily substance by the process sentence which followed process same as Production Example 2, this using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 2-(tert-butyldimethylsiloxy-3-hydroxy) butane and 2-aminothiazole made these and conventional method, and $ causing.

^{1}H-NMR ($CDCl_3$) δ : 1.25 (s, 3H, J = 6.2 Hz), 1.28 (s, 3H, J = 6.2 Hz), 3.08 (s, 3H), 3.87 (m, 1H), 4.22 (m, 1H), 6.85 (m, 1H), 6.99 (m, 1H), 7.13 (d, 2H, J = 8.8 Hz), 7.23 (m, 2H), 7.38 (m, 1H), 7.92 (d, 2H, J = 8.8 Hz), 12,0(br, 1H).

ESI-MS (m/e) = 463 $(M+H)^+$

Production Example 49



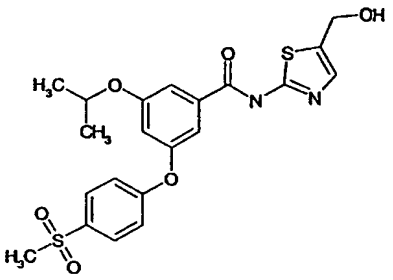
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl)-3-(4-methanesulphonyl phenoxy)-benzamide

The compound of Production Example 49 was obtained as a white amorphous substance using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 3-aminooxazole.

^{1}H-NMR ($CDCl_3$) δ : 1.32 (d, 3H, J = 6.0 Hz), 2.04 (m, 1H), 3.08 (s, 3H), 3.77 (m, 2H), 4.60 (m, 1H), 6.87 (m, 1H), 7.15 (d, 2H, J = 8.8 Hz), 7.19 (m, 2H), 7.35 (m, 1H), 7.94 (d, 2H, J = 8.8 Hz), 8.30 (d, 1H, J = 1.6 Hz), 9.24 (m, 1H).

ESI-MS (m/e) = 433 $(M+H)^+$

Production Example 50



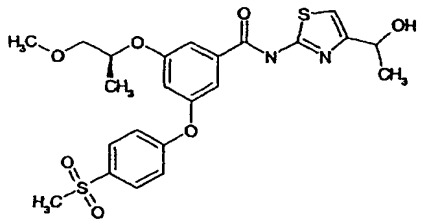
Preparation of N-(5-hydroxymethyl-thiazol-2-yl)-5-isopropoxy-3-(4-methanesulphonyl phenoxy)-benzamide

The compound of Production Example 50 was obtained as a straw-coloured oily substance using the same process as in Production Example 1, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 2-bromopropane and 2-amino-5-formyl thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.36 (d, 6H, J = 6.0 Hz), 3.08 (s, 3H), 4.59 (septet, 1H, J = 6.0 Hz), 4.79 (s, 2H), 6.82 (s, 1H), 7.14 (d, 2H, J = 8.4 Hz), 7.13-1.18 (m, 2H), 7.31 (s, 1H), 7.92 (d, 2H, J = 8.4 Hz), 11.2(br, 1H).

ESI-MS (m/e) = 463 $(M+H)^+$

Production Example 51



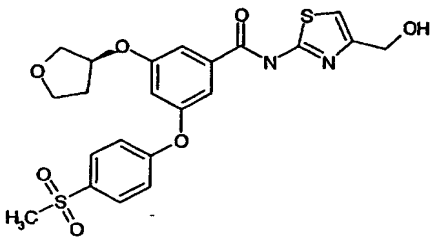
Preparation of N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonyl phenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide

The compound of Production Example 51 was obtained as a colourless amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-methoxy-2-hydroxy-propane and 2-amino-4-(1-tert-butyldimethylsiloxy ethyl) thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.35 (3H, d, J = 6.3 Hz), 1.55 (3H, d, J = 6.3 Hz), 3.08 (3H, s), 3.41 (3H, s), 3.49-3.64 (2H, m), 4.59-4.70 (1H, m), 4.90 (1H, q, J = 6.3 Hz), 6.80 (1H, brs), 6.90 (1H, br), 7.16 (2H, d, J = 8.9 Hz), 7.23-7.26 (1H, br), 7.42 (1H, brs), 7.94 (2H, d, J = 8.9 Hz).

ESI-MS (m/e) = 507 $(M+H)^+$

Production Example 52



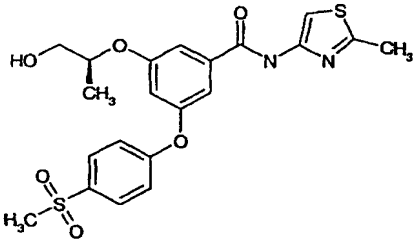
Preparation of N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonyl phenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide

The compound of Production Example 52 was obtained as a colourless amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 3-hydroxy-tetrahydrofuran and 2-amino-4-tert-butyldimethylsiloxy methylthiazole.

^{1}H-NMR ($CDCl_3$) δ : 2.10-2.36 (2H, m), 3.09 (3H, s), 3.39-4.07 (4H, m), 4.66 (2H, s), 4.96-5.05 (1H, m), 6.84 (1H, t.J= 2.0 Hz), 7.15-7.20 (3H, m), 7.30 (1H, .br), 7.96 (2H, d, J = 8.8 Hz).

ESI-MS (m/e) = 491 $(M+H)^+$

Production Example 53



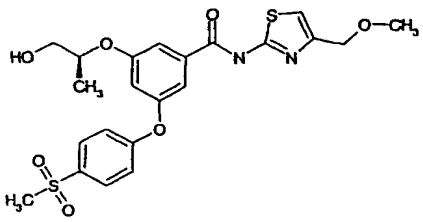
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-(2-methylthiazol-4-yl)-benzamide

The compound of Production Example 53 was obtained as a white amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 4-amino-2-methylthiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.32 (d, 3H, J = 6.0 Hz), 2.31 (m, 1H), 2.66 (s, 3H), 3.09 (s, 3H), 3.78 (m, 2H), 4.59(in, 1H), 7.13-7.16 (m, 1H), 7.15 (d, 2H, J = 8.8 Hz), 7.32 (m, 1H), 7.60 (s, 1H), 7.94 (d, 2H, J = 8.8 Hz), 8.90 (m, 1H).

ESI-MS (m/e) = 463 $(M+H)^+$

Production Example 54



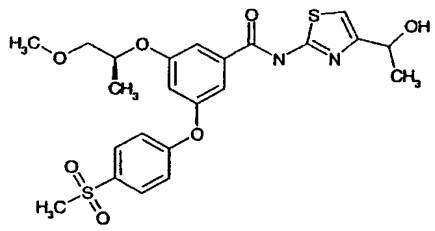
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-(4-methoxymethyl-thiazol-2-yl)-benzamide

The compound of Production Example 54 was obtained as a white amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 2-amino-4-methoxymethyl thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.31 (d, 3H, J = 6.0 Hz), 3.09 (s, 3H), 3.42 (s, 3H), 3.78 (m, 2H), 4.44 (m, 2H), 4.57 (m, 1H), 6.86 (m, 1H), 6.91 (s, 1H), 7.10-7.26 (m, 3H), 7.31 (m, 1H), 7.97 (d, 2H, J = 8.9 Hz), 9.67 (m, 1H).

ESI-MS (m/e) = 493 $(M+H)^+$

Production Example 55



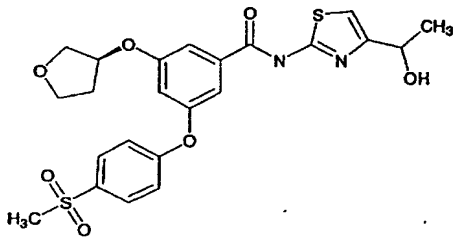
Preparation of N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonyl phenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide (diastereoisomer of Production Example 51)

The compound of Production Example 55 was obtained as a colourless amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 2-hydroxy-1-methoxy propane and 2-amino-4-(1-tert-butyldimethylsiloxy ethyl) thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.35 (3H, d, J = 6.3 Hz) 1.55 (3H, d, J = 6.3 Hz), 3.08 (3H, s), 3.41 (3H, s), 3.49-3.64 (2H, m), 4.59-4.70 (1H, m), 4.90 (1H, q, J = 6.3 Hz), 6.80 (1H, brs), 6.90 (1H, br), 7.16 (2H, d, J = 8.9 Hz), 7.23-7.26 (1H, br), 7.42 (1H, brs), 7.94 (2H, d, J = 8.9 Hz).

ESI-MS (m/e) = 507 $(M+H)^+$

Production Example 56



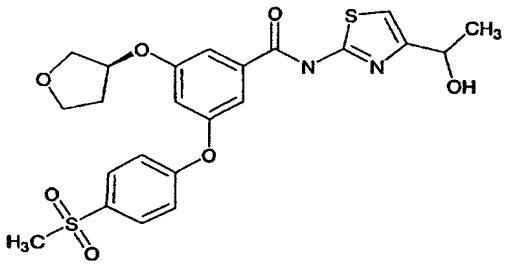
Preparation of N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonyl phenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide

The compound of Production Example 56 was obtained as white solid using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 3-hydroxytetrahydrofuran and 2-amino-4-(1-tert-butyldimethylsiloxy ethyl) thiazole.

^{1}H-NMR ($CDCl_3$) δ : 2.10-2.36 (2H, m), 0.39 (3H, s), 3.89-4.07 (4H, m), 4.85-4.95 (1H, m), 4.97-5.04 (1H, m), 6.81-6.85 (2H, m), 7.16 (2H, d, J = 8.7 Hz), 7.23 (1H, brs), 7.34 (1H, brs), 7.96 (2H, d, J = 8.7 Hz).

ESI-MS (m/e) = 505 $(M+H)^+$

Production Example 57



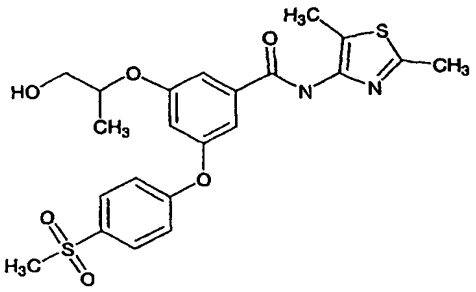
Preparation of N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonyl phenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide (diastereoisomer of Production Example 56)

The compound of Production Example 57 was obtained as white solid using the same process as in Production Example 56, a procedure in accordance with this or a combination of such procedures.

^{1}H-NMR ($CDCl_3$) δ : 2.10-2.35 (2H, m), 3.09 (3H, s), 3.89-4.06 (4H, m), 4.86-4.95 (1H, m), 4.97-5.05 (1H, m), 6.81-6.85 (2H, m), 7.16 (2H, d, J = 8.7 Hz), 7.22 (1H, brs), 7.34 (1H, brs), 7.96 (2H, d, J = 8.7 Hz).

ESI-MS (m/e) = 505 $(M+H)^+$

Production Example 58



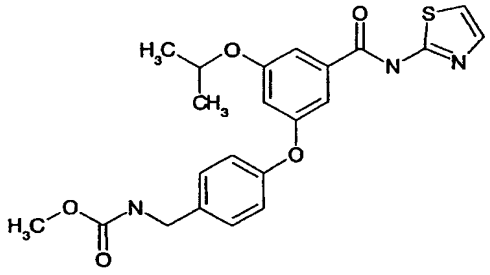
Preparation of N-(2,5-dimethyl thiazol-4-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-benzamide

The compound of Production Example 58 was obtained as a straw-coloured oily substance using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 4-amino-2,5-dimethyl thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.28 (d, 3H, J = 6.0 Hz), 2.32 (s, 3H), 2.56 (s, 3H), 3.07 (s, 3H), 3.72 (m, 2H), 4.53 (m, 1H), 6.79 (t, 1H, J = 2.0 Hz), 7.08 (dd, 2H, J = 2.0, 6.8 Hz), 7.18 (s, 1H), 7.32 (s, 1H), 7.89 (dd, 2H, J = 2.0, 6.8 Hz), 8.67 (m, 1H).

ESI... MS(m/e) = 477 $(M+H)^+$

Production Example 59



Preparation of 5-isopropoxy-3-(4-methoxycarbonylamino methylphenoxy)-N-thiazol-2-yl-benzamide

Potassium carbonate 41.0 g (0.30 mmol) and 2-bromopropane 23.8 g (0.19 mmol) were added to N,N-dimethylformamide solution (250 ml) of 3,5-dihydroxybenzoic acid methyl ester 25.0 g (0.15 mol), and thereafter the reaction liquor was stirred at 80°C for four hours. Water was added to the reaction liquid, extraction was carried out with ethyl acetate, the organic layer was washed with saturated aqueous sodium chloride solution, and after drying, it was concentrated under reduced pressure. The obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 5 : 1) and 5-hydroxy-3-isopropoxy benzoic acid methyl ester 12.0 g (yield = 38%) were obtained as a colourless oily substance.

Molecular sieve 4A 1.05g, p-formylphenyl boric acid 1.00 g (6.70 mol), copper acetate(II) 605mg (3.30 mol) and triethylamine 2.32 ml (16.6 mol) were added to methylene chloride solution (30 ml) of the obtained phenol body 700 mg (3.30 mmol), and thereafter, it was stirred at room temperature under oxygen atmosphere overnight. The reaction liquor was filtered, and thereafter concentrated under reduced pressure and the obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 5 : 1) and 3-(4-formyl phenoxy)-5-isopropoxy benzoic acid methyl ester 593 mg (yield = 57%) were obtained as a colourless oily substance.

Sodium borohydride 85.0 mg (2.25 mmol) was added to methanol solution (20 ml) of the obtained formyl body 590 mg (1.88 mmol), and thereafter the reaction liquor was stirred at room temperature for 16 hours. The reaction liquor was concentrated, and thereafter, saturated aqueous sodium bicarbonate solution was added and was extracted with chloroform, and the organic layer was dried, and thereafter concentrated under reduced pressure. The obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 2 : 1) and 3-(4-hydroxymethyl phenoxy)-5-isopropoxy benzoic acid methyl ester 567 mg (yield = 95%) were obtained as a colourless oily substance.

To chloroform solution (10 ml) of the obtained alcohol body 200 mg (0.63 mmol), triethylamine 0.18 ml (1.26 mmol) and methane sulphonyl chloride 0.073 ml (0.95 mmol) were added, and the reaction liquor was stirred at 50°C for ten minutes. Saturated aqueous sodium bicarbonate solution was added to the reaction liquid and the liquid extracted with chloroform, and the organic layer was dried, and thereafter concentrated under reduced pressure. DMF 5.0 ml were added to the obtained residue and were dissolved, and sodium azide 123 mg (1.90 mmol) was added and was stirred at 80°C for one hour. Water was added to the reaction liquid, extraction was carried out with ethyl acetate, the organic layer was dried, and thereafter concentrated under reduced pressure, and crude product of azide body was obtained.

Triphenyl phosphine 247 mg (1.26 mmol) was added to tetrahydrofuran-water (10 : 1) solution (11 ml) of the obtained azide body, and the reaction liquor was stirred at 90°C for 14 hours. 2N hydrochloric acid aqueous solution was added to the reaction liquor, and acidic aqueous solution was made. This solution was washed with ethyl acetate, and thereafter, 4N sodium hydroxide aqueous solution was added to the aqueous layer and basic aqueous solution formed, and thereafter, extraction with chloroform was carried out, and the organic layer was dried, and thereafter concentrated under reduced pressure, and aminic body was obtained 67.8 mg (yield = 34%) as crude product.

To chloroform solution (5.0 ml) of the obtained aminic body, chloro formic acid methyl ester 0.024

ml and triethylamine (0.057 ml, 0.41 mmol) were added, and the mixture was stirred at room temperature for one hour. Saturated aqueous sodium bicarbonate solution was added to the reaction liquor, and thereafter, extraction with chloroform was carried out, and the organic layer was dried, and thereafter concentrated under reduced pressure, and methoxycarbonylamino methyl body was obtained as crude product.

To tetrahydrofuran-methanol (5 : 3) solution (8.0 ml) of the obtained methoxycarbonylamino methyl body, 4N sodium hydroxide aqueous solution 1.0 ml (4.00 mmol) was added, and the reaction liquor was stirred at 50°C in the evening. Saturated ammonium chloride aqueous solution was added to the reaction liquor, and extraction with chloroform was carried out, and the organic layer was dried, and thereafter concentrated under reduced pressure and the obtained residue was refined using silica gel column chromatography (chloroform : methanol = 30 : 1) and 5-isopropoxy-3-(4 $ methoxycarbonylamino methylphenoxy)-benzoic acid 63.1 mg (yield = 85%) were obtained as white solid.

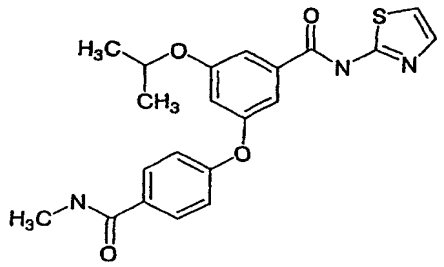
2-aminothiazole 33.0 mg (0.33 mol), 1-hydroxybenzotriazole hydrate 76.0 mg (0.49 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride 63.0 mg (0.33 mol) were added to N,N-dimethylformamide solution (3.0 ml) of the obtained carboxyl body, and thereafter, was stirred at room temperature overnight. Water was added to the reaction liquid, extraction was carried out with ethyl acetate, the reaction liquor was concentrated under reduced pressure and the obtained residue was refined using silica gel column chromatography (chloroform : methanol = 100 : 1) and the title compound was obtained as white solid. Analysis data of the compound obtained by Production Example 59 are shown below.

1HNMR ($CDCl_3$) δ : 1.34 (6H, d, J = 6.0 Hz), 3.71 (3H, s), 4.36 (2H, d, J = 5.5 Hz), 4.57 (1H, m), 4.99-5.10 (1H, br), 6.75 (1H, brs), 6.96-7.05 (4H, m), 7.20 (1H, br), 7.27-7.34 (3H, m), 10.70-10.88 (1H, 1).

ESI-MS(m/e)= 442 $(M+H)^+$

Using the same process as in the aforesaid Production Example 59, the compound of Production Example 60 to 64 was obtained. Below structure and analysis data of these compounds are shown.

Production Example 60



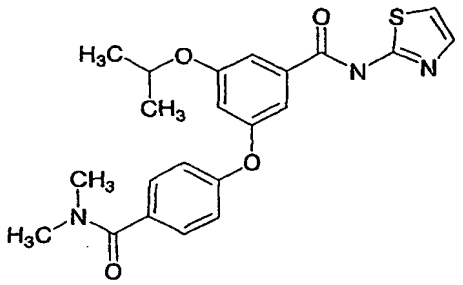
Preparation of 5-isopropoxy-3-(4-methylcarbamoyl-phenoxy)-N-thiazol-2-yl-benzamide

The compound of Production Example 60 was obtained as a colourless amorphous material using the same process as in Production Example 2, a procedure in accordance with this or similar such process, from 2-aminothiazole and 3-(4-methylcarbamoyl-phenoxy)-5 - isopropoxy benzoic acid methyl ester obtained by condensation reaction of methylamine with 3-(4-carboxy phenoxy)-5-isopropoxy benzoic acid methyl ester obtained by the oxidation of the formyl group of 3-(4-formyl phenoxy)-5-isopropoxy benzoic acid methyl ester obtained by Production Example 59.

^{1}H-NMR ($CDCl_3$) δ : 1.36 (6H, d, J = 6.1 Hz), 3.00 (3H, d, J = 4.8 Hz), 4.58 (1H, m), 6.12-6.21 (1H, br), 6.79 (1H, t.J= 2.2 Hz), 6.99-7.06 (4H, m), 7.24-7.27 (1H, m), 7.34 (1H, d, J = 3.6 Hz), 7.72 (2H, m).

ESI-MS (m/e) = 412 $(M+H)^+$

Production Example 61



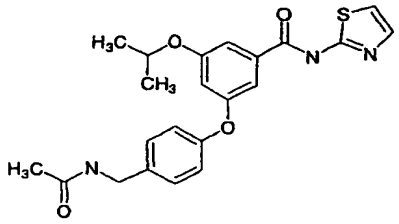
Preparation of 3-(4-dimethylcarbamoyl-phenoxy)-5-isopropoxy-N-thiazol-2-yl-benzamide

The compound of Production Example 61 was obtained as a colourless amorphous material using the same process as in Production Example 60, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-carboxyl phenoxy)-5-isopropoxy benzoic acid methyl ester obtained by Production Example 60, dimethylamine and 2-aminothiazole.

^{1}H-NMR ($CDCl_3$) δ : 1-34 (6H, d, J = 6.0 Hz), 2.98-3.15 (6H, br), 4.56 (1H, m), 6.78 (1H, t, J = 2.3 Hz), 6.98 (1H, d, J = 3.6 Hz), 7.00-7.06 (2H, m), 7.14-7.17 (1H, in), 7.24-7.28 (2H, m), 7.40-7.47 (2H, m).

ESI-MS (m/e) = 426 $(M+H)^+$

Production Example 62



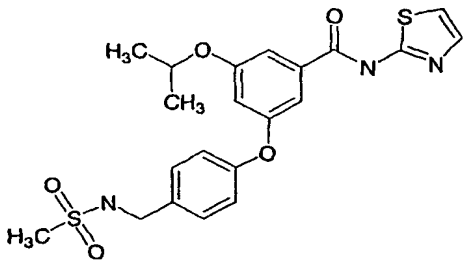
Preparation of 5-isopropoxy-3-(4-methyl carbonylamino methyl-phenoxy)-N-thiazol-2-yl-benzamide

Using 3-(4-aminomethyl phenoxy)-5-isopropoxy benzoic acid methyl ester obtained by Production Example 59, acetyl chloride and 2-aminothiazole, the compound was obtained as an colourless amorphous material by carrying out a production using the same process as in Production Example 59, a procedure in accordance with this or a combination of these and conventional procedures.

^{1}H-NMR ($CDCl_3$) δ : 1.35 (6H, d, J = 6.0 Hz), 2.05 (3H, s), 4.40 (2H, d, J = 5.6 Hz), 4.57 (1H, m), 5.95-6.07 (1H, br), 6.78 (1H, t, J = 2.2 Hz), 6.93-7.02 (4H, m), 7.20-7.32 (4H, 4).

ESI-MS (m/e) = 426 $(M+H)^+$

Production Example 63



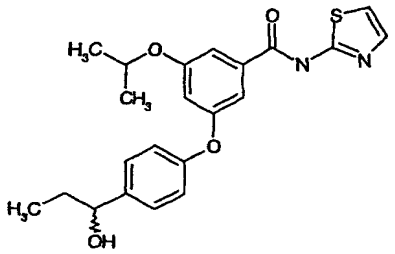
Preparation of 5-isopropoxy-3-(4-methanesulphonyl aminomethyl-phenoxy)-N-thiazol-2-yl-benzamide.

The compound of Production Example 63 was obtained as a colourless amorphous material using the same process as in Production Example 59, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-aminomethyl phenoxy)-5-isopropoxy benzoic acid methyl ester obtained by Production Example 59, methanesulfonyl chloride and 2-aminothiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.36 (6H, d, J = 6.0 Hz), 2.94 (3H, s), 4.32 (2H, d, J = 6.1 Hz), 4.60 (1H, m), 4.79-4.88 (1H, m), 6.77(1H, m), 6.98-7.38 (8H, m).

ESI-MS (m/e) = 462 $(M+H)^+$

Production Example 64



Preparation of 3-[4-(1-hydroxy-propyl)-phenoxy]-5-isopropoxy-N-thiazol-2-yl-benzamide

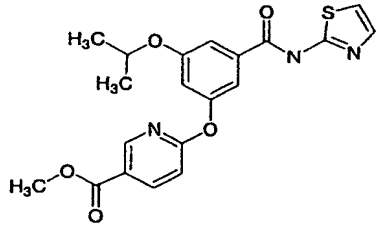
The compound of Production Example 64 was obtained as a colourless amorphous material using the same process as in Production Example 59, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-formyl phenoxy)-5-isopropoxy benzoic acid methyl ester obtained by Production Example 59, ethyl magnesium bromide and 2-aminothiazole.

Moreover, the reaction of the ethyl magnesium bromide with 3-(4-formyl phenoxy)-5-isopropoxy benzoic acid methyl ester, was a so-called Grignard reaction, and was carried out in accordance with a a process in accordance with literature (for example, Comprehensive Organic Transformations, Richard L, VCH Publishers Co, 1988 and the like), a procedure in accordance with this or a combination of these and conventional procedures.

^{1}H-NMR ($CDCl_3$) δ : 0.92 (3H, t, J = 7.4 Hz), 1.34 (6H, d, J = 6.1 Hz), 1.67-1.88 (2H, m), 4.51-4.63 (2H, m), 6.76 (1H, t, J = 2.3 Hz), 6.95-7.07 (3H, m), 7.04-7.07 (1H, m), 7.20-7.24 (2H, m), 7.32 (2H, d, J = 8.5 Hz).

ESI-MS (m/e) = 413 $(M+H)^+$

Production Example 65



Preparation of 6-[3-isopropoxy-5-(thiazol-2-yl carbamoyl)-phenoxy]-nicotinic acid methyl ester

4N sodium hydroxide aqueous solution 10 ml were added to methanol solution (50 ml) of 5-hydroxy-3-isopropoxy benzoic acid methyl ester 3.0 g obtained by Production Example 59 (14.3 mmol), and the mixture was stirred at room temperature for 12 hours. The reaction liquor was concentrated under reduced pressure, and thereafter, saturated ammonium chloride aqueous solution was added, and extraction with chloroform was carried out, and it was dried, and thereafter the organic layer was concentrated under reduced pressure. The obtained residue was refined using

silica gel chromatography (chloroform : methanol = 50 : 1) and 5-hydroxy-3-isopropoxy benzoic acid 2.44 g (yield = 87%) were obtained as a white solid.

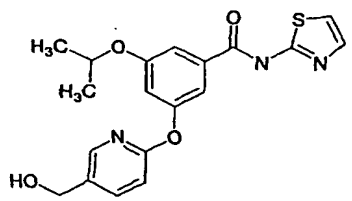
To chloroform solution (50 ml) of the obtained carboxylic acid 2.40 g (12.2 mmol), 2-aminothiazole 2.45 g (24.5 mmol), triethylamine 3.40 ml (24.5 mmol), 2-chloro-1,3-dimethyl imidazolinium chloride 4.14 g (24.5 mmol) were added under ice cooling, and the mixture was stirred at room temperature for 13 hours. Saturated ammonium chloride aqueous solution was added to the reaction liquor, and extraction with chloroform was carried out, and the organic layer was dried, and thereafter concentrated under reduced pressure. 4N sodium hydroxide aqueous solution 10 ml were added to methanol solution (40 ml) of the obtained residue, and the mixture was stirred at room temperature for one hour. The reaction liquor was concentrated under reduced pressure, and thereafter, saturated ammonium chloride aqueous solution was added, and extraction with chloroform was carried out, and it was dried, and thereafter the organic layer was concentrated under reduced pressure. The obtained residue was refined using silica gel chromatography (chloroform : methanol = 100 : 1) and 5-hydroxy-3-isopropoxy-N-thiazol-2-yl-benzamide 1.81 g (yield = 53%) were obtained as a white solid.

To N,N-dimethylformamide solution (10.0 ml) of the obtained amide body 100 mg (0.36 mmol), 6-chloro nicotinic acid methyl ester 123 mg (0.72 mmol), potassium carbonate 199 mg (1.44 mmol) were added and thereafter, under a nitrogen atmosphere, were stirred at 80°C for 18 hours. Water was added to the reaction liquid and the extraction was carried out with ethyl acetate, and the organic layer was dried, and thereafter concentrated under reduced pressure. The obtained residue was refined using silica gel chromatography (hexane : ethyl acetate = 3 : 1) and the title compound was obtained as a white solid. Analysis data of the compound obtained by Production Example 65 are shown below.

^{1}H-NMR ($CDCl_3$) δ : 1.36 (6H, d, J = 6.0 Hz), 3.93 (3H, s), 4.60 (1H, m), 6.91-7.02 (3H, m), 7.29-7.40 (3H, m), 8.31 (1H, dd, J = 8.6, 2.4 Hz), 8.81 (1H, d, J = 2.4 Hz).

ESI-MS (m/e) = 414[M+H] +.

Production Example 66



Preparation of 3-(5-hydroxymethyl-pyridin-2-yl-oxy)-5-isopropoxy-N-thiazol-2-yl-benzamide

Lithium aluminium hydride 6.0 mg (0.16 mmol) was added under ice cooling to tetrahydrofuran

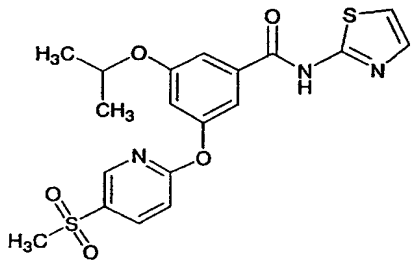
solution (5.0 ml) of 6-[3-isopropoxy-5-(thiazol-2-yl carbamoyl)-phenoxy] - nicotinic acid methyl ester 60.0 mg obtained by Production Example 65 (0.15 mmol) and was stirred at 0°C for one hour. Saturated aqueous sodium bicarbonate solution was added to the reaction liquor, and extraction with ethyl acetate was carried out, and the organic layer was dried, and thereafter concentrated under reduced pressure. The obtained residue was refined using silica gel chromatography (chloroform : methanol = 30 : 1) and the title compound was obtained as a white solid. Below analysis data of the compound obtained by Production Example 66 are shown.

^{1}H-NMR ($CDCl_3$) δ : 1.36 (6H, d, J = 6.0 Hz), 4.54-4.64 (1H, m), 4.68 (2H, s), 6.90 (1H, t, J = 2.1 Hz), 6.92-6.98 (2H, m), 7.22 (1H, t, J = 1.7 Hz), 7.31-7.37 (2H, m), 7.77 (1H, dd, J = 2.8, 8.3 Hz), 8.14 (1H, br).

ESI-MS(m/e)= 386 (M+H)+.

Using procedures of the aforesaid Production Example 65 or 66, the compound of Production Example 67 to 73 were obtained. Below analysis data of these compounds is shown.

Production Example 67



Preparation of 5-isopropoxy-3-(5-methanesulphonyl pyridin-2-yl)-N-thiazol-2-yl-benzamide

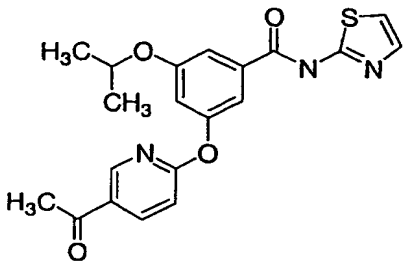
The compound of Production Example 67 was obtained as a straw-coloured oily substance using the same process as in Production Example 65, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-isopropoxy-N-thiazol-2-yl-benzamide obtained by Production Example 65 and 2,5-bis methanesulphonyl pyridine.

Moreover, 2,5-bis methanesulphonyl pyridine was obtained by reacted 2,5-dibromo pyridine with sodium thio methoxide to form 2,5-bis-methylthio pyridine and thereafter oxidising with metachloro perbenzoic acid. The reaction of 2,5-bis-methylthio pyridine with sodium methoxide of the reaction of metachloro perbenzoic acid with 2,5-dibromo pyridine were carried out in accordance with conventional method.

^{1}H-NMR ($CDCl_3$) δ : 1.37 (6H, d, J = 6, IHz), 3.11 (3H, s), 4.58-4.66 (1H, m), 6.93 (1H, t, J = 1.8 Hz), 6.99 (1H, d, J = 3.6 Hz), 7.12 (1H, d, J = 8.7 Hz), 7.29 (1H, d, J = 1.8 Hz), 7.36 (1H, d, J = 3.6 Hz), 7.40 (1H, d, J = 1.8 Hz), 8.21 (1H, dd, J = 2.6, 8.7 Hz), 8.71 (1H, d, J = 2.6 Hz).

ESI-MS (m/e) = 434 $(M+H)^+$

Production Example 68



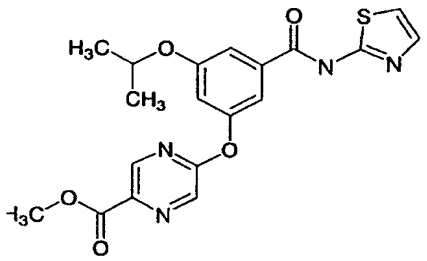
Preparation of 3-(5-acetyl-pyridin-2-yl-oxy)-5-isopropoxy-N-thiazol-2-yl-benzamide

The compound of Production Example 68 was obtained as white solid using the same process as in Production Example 65, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-isopropoxy-N-thiazol-2-yl-benzamide obtained using the same process as in Production Example 65 and 2-chloro-5-acetylpyridine.

^{1}H-NMR ($CDCl_3$) δ : 1.37 (6H, d, J = 6.0 Hz), 2.59 (3H, s), 4.61 (1H, m), 6.93 (1H, t, J = 2.1 Hz), 6.98 (1H, d, J = 3.6 Hz), 7.04 (1H, d, J = 8.6 Hz), 7.29 (1H, t, J = 2.1 Hz), 7.38 (2H, m), 8.30 (1H, dd, J = 2.5, 8.6Hz), 8.75 (1H, d, J = 2.5Hz).

ESI-MS (m/e) = 398 $(M+H)^+$

Production Example 69



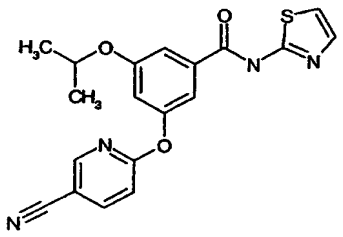
Preparation of 5-isopropoxy-3-(5-methoxycarbonyl-pyrazin-2-yl-oxy)-N-thiazol-2-yl-benzamide

The compound of Production Example 69 was obtained as a colourless amorphous material using the same process as in Production Example 65, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-isopropoxy-N-thiazol-2-yl-benzamide obtained using the same process as in Production Example 65 and 2-chloro-5-methoxycarbonyl pyrazine.

^{1}H-NMR ($CDCl_3$) δ : 1.38 (6H, d, J = 6.0 Hz), 4.03 (3H, s), 4.57-4.65 (1H, m), 6.95 (1H, t, J = 2.1 Hz), 7.00 (1H, d, J = 3.6 Hz), 7.33-7.35 (1H, m), 7.37-7.42 (2H, m), 8.54 (1H, d, J = 1.2 Hz), 8.85 (1H, d, J = 1.2 Hz).

ESI-MS (m/e) = 415 $(M+H)^+$

Production Example 70



Preparation of 3-(5-cyano-pyridin-2-yl-oxy)-5-isopropoxy-N-thiazol-2-yl-benzamide

The compound of Production Example 70 was obtained as a colourless amorphous material by reacting copper cyanide (1) with 3-(5-bromo-pyridin-2-yl-oxy)-5-isopropoxy-N-thiazol-2-yl-benzamide obtained by the same method as in Production Example 65, using 2,5-dibromo pyridine and

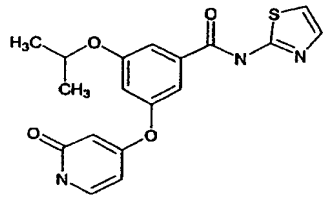
5-hydroxy-3-isopropoxy-N-thiazol-2-yl-benzamide obtained by the same method as in Production Example 65.

Moreover, the reaction of 3-(5-bromo-pyridin-2-yl-oxy)-5-isopropyl-N-thiazol-2-yl-benzamide and copper cyanide, was carried out in accordance with literature methods (for example Comprehensive Organic Transformations, Richard L et al, VCH Publishers Co, 1988 and the like), a procedure in accordance with this or a combination of these and conventional procedures.

^{1}H-NMR ($CDCl_3$) δ : 1.37 (6H, d, J = 6.1 Hz), 4.61 (1H, m), 6.89-6.92 (1H, m), 6.97-7.01 (1H, m), 7.06-7.09 (1H, m), 7.26-7.29 (1H, m), 7.35-7.40 (1H, m), 7.93-7.98 (1H, m), 8.47-8.49 (1H, m).

ESI-MS (m/e) = 381 $(M+H)^+$

Production Example 71



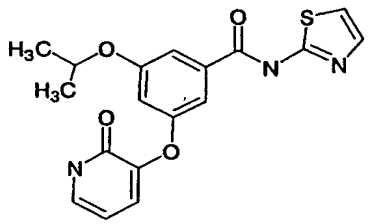
Preparation of 5-isopropoxy-3-(2-oxo-1,2-dihydro-pyridin-4-yl-oxy)-N-thiazol-2-yl-benzamide

The compound of Production Example 71 was obtained as white solid using the same process as in Production Example 65, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-isopropoxy benzoic acid methyl ester obtained using the same process as in Production Example 59, 4-bromo-pyridine hydrochloride and 2-aminothiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.31 (6H, d, J = 6.0 Hz), 4.73-4.83 (1H, m), 5.51 (1H, d, J = 2.6 Hz), 6.03 (1H, dd, J = 2.5, 7.4 Hz), 6.99 (1H, t, J = 2.2 Hz), 7.30 (1H, d, J = 3.6 Hz), 7.38-7.44 (2H, m), 7.55-7.59 (2H, m).

ESI-MS (m/e) = 372(M+H) +.

Production Example 72



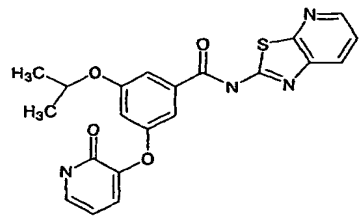
Preparation of 5-isopropoxy-3-(2-oxo-1,2-dihydro-pyridin-3-yl-oxy)-N-thiazol-2-yl-benzamide

The compound of Production Example 72 was obtained as white crystal using the same process as in Production Example 65, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-isopropoxy benzoic acid methyl ester obtained using the same process as in Production Example 59, 3-bromo-2-hydroxy-pyridine and 2-aminothiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.34 (6H, d, J = 6.0 Hz), 4.62-4.72 (1H, m), 6.41 (1H, dd, J = 6.7, 7.2 Hz), 6.76 (1H, t, J = 2.3 Hz), 7.10-7.13 (1H, dd, J = 1.5, 2.2 Hz), 7.14 (1H, d, J = 3.6 Hz), 7.27-7.29 (1H, m), 7.30-7.37 (2H, m), 7.48 (2H, d, J = 3.6 Hz).

ESI-MS (m/e) = 372 $(M+H)^+$

Production Example 73



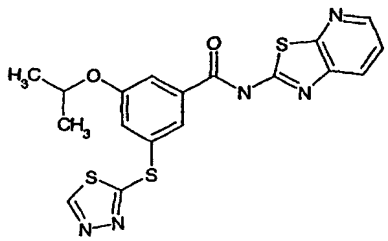
Preparation of 5-isopropoxy-3-(2-oxo-1,2-dihydro-pyridin-3-yl-oxy)-N-thiazolo [5,4-b] pyridin-2-yl-benzamide

The compound of Production Example 73 was obtained as white solid using the same process as in Production Example 65, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-isopropoxy benzoic acid methyl ester obtained using the same process as in Production Example 59, 3-bromo-2-hydroxy-pyridine and 2-amino-thiazolo [5,4-b] pyridine.

^{1}H-NMR ($CDCl_3$) δ : 1.31 (6H, d, J = 6.0 Hz), 4.68-4.81 (1H, m), 6.25 (1H, t, J = 6.9 Hz), 6.68-6.72 (1H, m), 7.13-7.16 (1H, m), 7.31-7.40 (2H, m), 7.44-7.54 (2H, m), 8.12 (1H, d, J = 7.8 Hz), 8.46-8.52 (1H, m).

ESI-MS (m/e) : 423 $(M+H)^+$

Production Example 74



Preparation of 5-isopropoxy-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazolo [5,4-b] one pyridine-2 yl-benzamide

Potassium carbonate 298 mg (2.16 mmol) and 2-bromopropane 0.12 ml (1.29 mmol) were added to N,N-dimethylformamide solution (4.0 ml) of 3-hydroxy-5-iodobenzoic acid methyl ester 120 mg (0.43 mol), and thereafter the reaction liquor was stirred at 80°C overnight. Water was added to the reaction liquid, extraction was carried out with ethyl acetate, the organic layer was washed with saturated aqueous sodium chloride solution, and after drying, it was concentrated under reduced pressure. The obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 5 : 1) and 5-iodo-3-isopropoxy benzoic acid methyl ester 133 mg (yield = 96%) were obtained as a colourless oily substance.

2-mercapto-1,3,4-thiadiazole 292 mg (2.47 mol), potassium carbonate 456 mg (3.30 mol), hydroquinone 27.0 mg (0.25 mmol) and copper bromide (1) 35.0 mg (0.25 mmol) were added to N,N-dimethylformamide solution (10 ml) of the obtained iodo body 132 mg (0.41 mmol), and thereafter, under a nitrogen atmosphere, it was stirred at 130°C for forty minutes. Water was added to the reaction liquid, extraction was carried out with ethyl acetate, the organic layer was washed with saturated aqueous sodium chloride solution, and after drying, it was concentrated under reduced pressure. The obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 1 : 1) and 5-isopropoxy-3-(1,3,4-thiadiazol-2-yl-thio) benzoic acid methyl ester 8.90 mg (yield = 7 %) were obtained as a colourless oily substance.

To methanol solution (1.0 ml) of the obtained ester, 2N sodium hydroxide aqueous solution 0.14 ml (0.29 mmol) was added, and the reaction liquor was stirred at room temperature for five hours. 2N hydrochloric acid aqueous solution was added to the reaction liquid, extraction was carried out with ethyl acetate, the organic layer was washed with saturated aqueous sodium chloride solution, and after drying, it was concentrated under reduced pressure, and crude product of carboxyl body was obtained.

2-amino-thiazolo [5,4-b]-pyridine 8.20 mg (0.054 mol), 1-hydroxybenzotriazole hydrate 5.00 mg

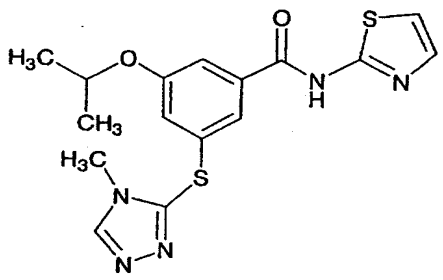
(0.037 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride 7.10 mg (0.037 mol) were added to N,N-dimethylformamide solution (1.2 ml) of the obtained carboxyl body, and thereafter, it was stirred at room temperature overnight. The reaction liquor was concentrated under reduced pressure and the obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 1 : 1) and the title compound was obtained as a white solid. Analysis data of the compound obtained by Production Example 74 are shown below.

^{1}H-NMR ($CDCl_3$) δ :1.32 (6H, d, J = 6.0 Hz), 4.54-4.62 (1H, m), 7.32 (1H, dd, J = 4.6, 8.2 Hz), 7.37 (1H, t, J = 1.8 Hz), 7.56 (1H, t, J = 1.8 Hz), 7.74 (1H, dd, J = 1.4, 8.2 Hz), 7.79 (1H, t, J = 1.8 Hz), 8.52 (1H, dd, J = 1.4, 4.6 Hz), 9.07 (1H, s).

ESI-MS(m/e)= 430 $(M+H)^+$.

Using the same process as in the aforesaid Production Example 74, the compounds of Production Example 75 to Production Example 88 were obtained. Below, among these compounds, analysis data of the representative usual compound is shown.

Production Example 75



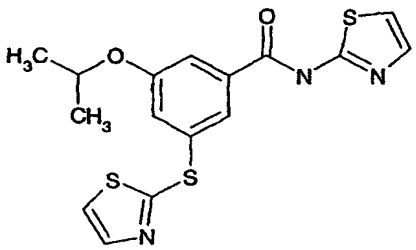
Preparation of 5-isopropoxy-3-(4-methyl-[1,2,4] triazol-3-yl sulphanyl)-N-thiazol-2-yl-benzamide

The compound of Production Example 75 was obtained as a colourless amorphous material using the same process as in Production Example 74, a procedure in accordance with this or a combination of these and conventional procedures, using 5-iodo-3-isopropoxy benzoic acid methyl ester obtained by Production Example 74, 2-aminothiazole and 3-mercapto-4-methyl-[1,2,4] triazole.

^{1}H-NMR ($CDCl_3$) δ : 1.31 (6H, d, J = 5.9 Hz), 3.65 (3H, s), 4.53-4.57 (1H, m), 6.98 (1H, q, J = 3.5 Hz), 7.06 (1H, s), 7.20 (1H, d, J = 3.5 Hz), 7.41 (1H, s), 7.53 (1H, s), 8.29 (1H, s).

ESI-MS (m/e) = 374 $(M-H)^-$.

Production Example 76

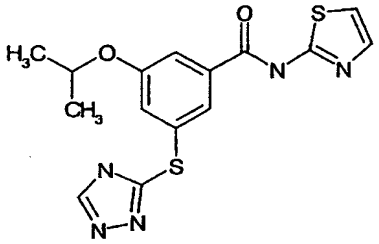


Preparation of 5-isopropoxy-3-thiazol-2-yl sulphanyl-N-thiazol-2-yl-benzamide

The compound of Production Example 76 was obtained as a colourless amorphous material using the same process as in Production Example 74, a procedure in accordance with this or a combination of these and conventional procedures, using 5-iodo-3-isopropoxy benzoic acid methyl ester-2-aminothiazole obtained by Production Example 75 and 2-mercapto-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.33 (6H, d, J = 6.0 Hz), 4.54-4.62 (1H, m), 6.95 (1H, d, J = 3.6 Hz), 7.15 (1H, d, J = 3.6 Hz), 7.29-7.32 (2H, m), 7.50 (1H, dd, J = 1.5, 2.2 Hz), 7.69 (1H, d, J = 1.5 Hz), 7.77 (1H, d, J = 3.4 Hz).

Production Example 77



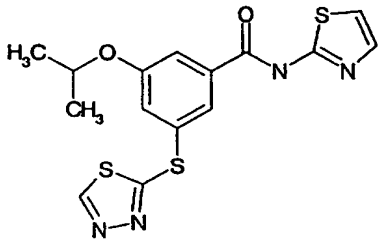
Preparation of 5-isopropoxy-3-(4H-[1,2,4] triazol-3-yl sulphanyl)-N-thiazol-2-yl-benzamide

The compound of Production Example 77 was obtained as a colourless amorphous material using the same process as in Production Example 74, a procedure in accordance with this or a combination of these and conventional procedures, using 5-iodo-3-isopropoxy benzoic acid methyl ester obtained by Production Example 74, 2-aminothiazole and 3-mercapto-[1,2,4] triazole.

^{1}H-NMR ($CDCl_3$) δ : 1.34 (6H, d, J = 6.0 Hz), 4.59-4.63 (1H, m), 7.04 (1H, d, J = 2.5 Hz), 7.44 (1H, dd, J = 1.0 Hz), 7.49 (1H, t, J = 1.0 Hz), 7.49 (1H, d, J = 2.5 Hz), 7.67 (1H, t, J = 1.0 Hz), 8.24 (1H, s).

ESI-MS (m/e) = 362 $(M+H)^+$

Production Example 78



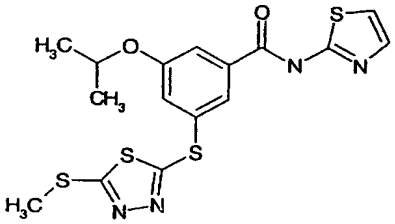
Preparation of 5-isopropoxy-3-([1,3,4] thiadiazol-2-yl sulfanyl)-N-thiazol-2-yl-benzamide

The compound of Production Example 78 was obtained as a colourless amorphous material using the same process as in Production Example 74, a procedure in accordance with this or a combination of these and conventional procedures, using 5-iodo-3-isopropoxy benzoic acid methyl ester obtained by Production Example 74, 2-aminothiazole and 2-mercapto-[1,3,4] thiadiazole.

^{1}H-NMR (CD_3OD) δ = 1.37 (6H, d, J = 6.0 Hz), 4.71-4.81 (1H, m), 7.14 (1H, d, J = 3.7 Hz), 7.45 (1H, t, J = 1.8 Hz), 7.50 (1H, d, J = 3.7 Hz), 7.68 (1H, t, J = 1.8 Hz), 7.89 (1H, t, J = 1.8 Hz), 9.32 (1H, s).

ESI-MS (m/e) = 379 $(M+H)^+$

Production Example 79



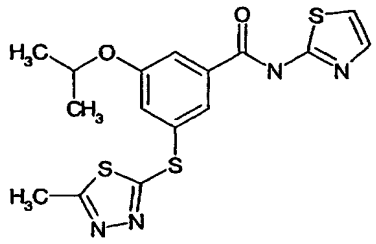
Preparation of 5-isopropoxy-3-(5-methyl sulphanyl-[1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide

The compound of Production Example 79 was obtained as a colourless oily substance using the same process as in Production Example 74, a procedure in accordance with this or a combination of these and conventional procedures, using 5-iodo-3-isopropoxy benzoic acid methyl ester obtained by Production Example 74, 2-aminothiazole and 2-mercapto-5-methyl sulphanyl-[1,3,4] thiadiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.34 (6H, d, J = 6.0 Hz), 2.75 (3H, s), 4.55-4.63 (1H, m), 6.97 (1H, d, J = 3.6 Hz), 7.13 (1H, d, J = 3.6 Hz), 7.32 (1H, t, J = 1.8 Hz), 7.53 (1H, t, J = 1.8 Hz), 7.72 (1H, t, J = 1.8 Hz).

ESI-MS (m/e) = 425 $(M+H)^+$

Production Example 80

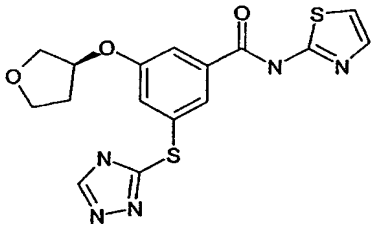


Preparation of 5-isopropoxy-3-(5-methyl-[1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide

The compound of Production Example 80 was obtained as a colourless amorphous material using the same process as in Production Example 74, a procedure in accordance with this or a combination of these and conventional procedures, using 5-iodo-3-isopropoxy benzoic acid methyl ester obtained by Production Example 74, 2-aminothiazole and 2-mercapto-5-methyl-[1,3,4] thiadiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.35 (6H, d, J = 6.0 Hz), 2.72 (3H, s), 4.56-4.64 (1H, m), 6.97 (1H, d, J = 3.6 Hz), 7.17 (1H, d, J = 3.6 Hz), 7.35 (1H, t, J = 1.8 Hz), 7.54 (1H, t, J = 1.8 Hz), 7.73 (1H, t, J = 1.8 Hz) ESI-MS (m/e) = 393 (M+H) +.

Production Example 81



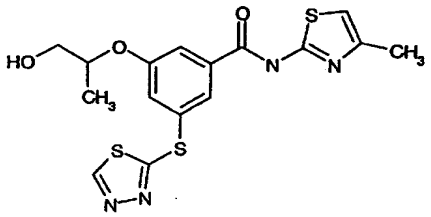
Preparation of 5-(tetrahydrofuran-3-yl-oxy)-N-thiazol-2-yl-3-(4H-[1,2,4] triazol-3-yl sulphanyl)-benzamide

The compound of Production Example 81 was obtained as a colourless oily substance using the same process as in Production Example 74, a procedure in accordance with this or a combination of these and conventional procedures, using 2-aminothiazole, 3-mercapto-[1,2,4] triazole and 5-iodo-3-(tetrahydrofuran-3-yloxy) benzoic acid methyl ester obtained by the same method as in Production Example 74, using (3R)-3-bromopropane instead of 2-bromopropane.

^{1}H-NMR ($CDCl_3$) δ : 2.05-2.24 (2H, m), 3.89-4.02 (4H, m), 4.94-4.98 (1H, m), 7.06 (1H, d, J = 3.6Hg), 7.23 (1H, t, J = 1.8Hg), 7.40 (1H, d, J = 1.8 Hz), 7.48 (1H, d, J = 3.6 Hz), 7.68 (1H, d, J = 1.8 Hz), 8.32 (1H, s).

ESI-MS (m/e) = 390 $(M+H)^+$

Production Example 82



Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-N-(4-methyl-thiazol-2-yl)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-benzamide

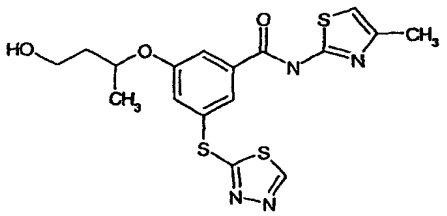
The compound of Production Example 82 was obtained a colourless oily substance using the same process as in Production Example 74, a procedure in accordance with this or a combination of these and conventional procedures, using 2-mercapto-[1,3,4] thiadiazole and 3-(2-tert-butyl-dimethyl siloxy-1-methyl-ethoxy)-5-iodo-N-(4-methyl-thiazol-2-yl)-benzamide obtained using the same process as in Production Example 65 using 3-hydroxy-5-iodo-benzoic acid methyl ester, 1-tert dimethyl siloxy-2-hydroxypropane and 2-amino-4-methyl-thiazole.

Moreover, removal of tert-butyldimethylsiloxy group which is protecting group of hydroxy group was carried out using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures.

^{1}H-NMR ($CDCl_3$) δ : 1.32 (d, 3H, J = 6.2 Hz), 2.38 (s, 3H), 4.79 (m, 2H), 4.65 (m, 1H), 6.63 (s, 1H), 7.38 (m, 1H), 7.72 (m, 1H), 7.82 (m, 1H), 9.08 (s, 1H).

ESI-MS (m/e) = 409 $(M+H)^+$

Production Example 83



Preparation of 5-(3-hydroxy-1-methyl-propoxy)-N-(4-methyl-thiazol-2-yl)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-benzamide

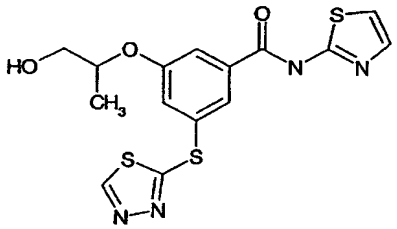
The compound of Production Example 83 was obtained as a white amorphous material using the same process as in Production Example 74, a procedure in accordance with this or a combination of these and conventional procedures, using 2-mercapto-[1,3,4] thiadiazole and 3-(3-tert-butyldimethylsiloxy-1-methyl-propoxy)-5-iodo-N-(4-methyl-thiazol-2-yl)-benzamide obtained using the same method as in Production Example 65 using 3-hydroxy-5-iodo-benzoic acid methyl ester, 5-tert-butyldimethylsiloxy-pentane-2-ol and 2-amino-4-methyl-thiazole. Moreover, removal of tert-butyldimethylsiloxy group which is the protecting group of hydroxy group was carried out

using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures,.

^{1}H-NMR ($CDCl_3$) δ : 1-33 (d, 3H, J = 6.1 Hz), 2.10-1.75 (m, 4H), 2.18 (d, 1H, J = 1.0 Hz), 3.78 (m, 2H), 4.63 (m, 1H), 6.56 (d, 1H, J = 1.0 Hz), 7.38 (m, 1H), 7.61 (m, 1H), 7.73 (m, 1H), 9.05 (s, 1H), 11.1(br, 1H).

ESI-MS (m/e) = 423 $(M+H)^+$

Production Example 84



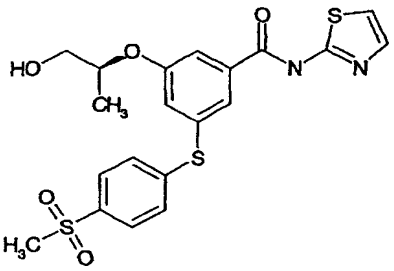
Preparation of 5-(2-hydroxy-1-methyl one ethoxy)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide

The compound of Production Example 84 was obtained as a colourless oily substance using the same process as in Production Example 74, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(2-tert-butyldimethylsiloxy-1-methyl-propoxy)-5-iodo-N- (thiazol-2-yl)-benzamide obtained using the same method as in Production Example 65 using 3-hydroxy-5-iodo-benzoic acid methyl ester, 1-tert butoxy-2-ol and 2-aminothiazole, 2-mercapto-[1,3,4] thiadiazole. Moreover, for the removal of tert-butyldimethylsiloxy group which are protecting group of hydroxy group, the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures may be used.

^{1}H-NMR ($CDCl_3$) δ : 1.30 (d, 3H, J = 6.0 Hz), 3.80 (m, 2H), 4.62 (sextet, 1H, J = 6.0 Hz), 7.00 (d, 1H, J = 3.6 Hz), 7.27 (d, 1H, J = 3.6 Hz), 7.40 (m, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 9.09 (s, 1H).

ESI... MS(m/e) = 395 $(M+H)^+$

Production Example 85



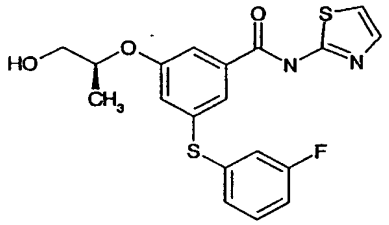
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenyl sulphanyl)-N-thiazol-2-yl-benzamide

The compound of Production Example 85 was obtained as a colourless oily substance using the same process as in Production Example 74, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(2-tert-butyldimethylsiloxy-1-methyl-propoxy)-5-iodo-N-(thiazol-2-yl)-benzamide obtained using the same method as in Production Example 65 using 3-hydroxy-5-iodo-benzoic acid methyl ester, 1-tert-butyldimethylsiloxy-butane-2-ol, 2-aminothiazole and 2-mercapto-[1,3,4] thiadiazole. Moreover, the removal of the tert-butyldimethylsiloxy group which is protecting group of hydroxy group, was carried out in accordance with the process of Production Example 2, a methoc in accordance with this or a combination of these and a conventional method.

^{1}H-NMR ($CDCl_3$) δ : 1.31 (d, 3H, J = 6.2 Hz), 3.07 (s, 3H), 3.78 (m, 2H), 4.58 (m, 1H), 7.01 (d, 1H, J = 3.6 Hz), 7.24 (m, 2H), 7.37 (d, 2H, J = 8.6 Hz), 7.55 (m, 1H), 7.61 (m, 1H), 7.84 (d, 2H, J = 8.6 Hz), 11.3(br, 1H).

ESI-MS (m/e) = 465 $(M+H)^+$

Production Example 86



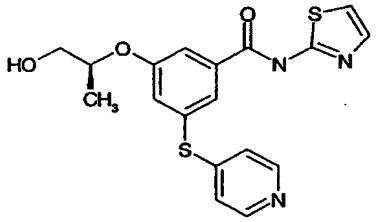
Preparation of 3-(3-fluoro-phenylthio)-5-(2-hydroxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide

The compound of Production Example 86 was obtained as a white amorphous substance by the same method as in Production Example 74, a process in accordance with this or combining these and conventional method using 3-fluoro thiophenol, 3-(2-tert-butyldimethylsiloxy-1-methyl-ethoxy)-5-iodo-N-(thiazol-2-yl)-benzamide obtained by the same method as in Production Example 65 using 3-hydroxy-5-iodo-benzoic acid methyl ester, 1-(tert dimethyl siloxy)-2-hydroxypropane and 2-aminothiazole. Moreover, removal of tert-butyldimethylsiloxy group which was a protecting group of hydroxy group was carried out by the same method as in Production Example 2, a process in accordance with this or a combination of this and a conventional method.

^{1}H-NMR ($CDCl_3$) δ : 1.27 (d, 3H, J = 6.2 Hz), 3.75 (m, 2H), 4.54 (m, 1H), 7.18-6.95 (m, 4H), 7.21 (m, 1H), 7.30 (m, 1H), 7.52-7.40 (m, 2H).

ESI-MS (m/e) = 405 $(M+H)^+$

Production Example 87



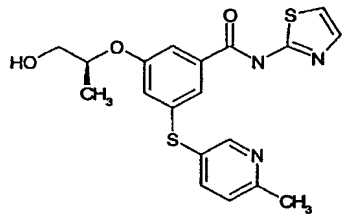
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(pyridin-4-yl sulphanyl)-N-thiazol-2-yl-benzamide

The compound of Production Example 87 was obtained as a yellow oily material by the same method as in Production Example 74, a process in accordance with this, or a combination of these and conventional method using 4-mercaptopyridine and 3-(2-tert-butyldimethylsiloxy-1-methyl-ethoxy)-5-iodo-N-(thiazole-2-yl)-benzamide obtained by the same method as in Production Example 65 using 3-hydroxy-5-iodo-benzoic acid methyl ester, 1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 2-aminothiazole. Moreover, the removal of tert-butyldimethylsiloxy group which was a protecting group of hydroxy group was carried out by the same method as in Production Example 2, a process in accordance with this, or a combination of these and conventional method.

^{1}H-NMR ($CDCl_3$) δ : 1.36 (d, 3H, J = 6.1 Hz), 3.72 (d, 2H, J = 6.1 Hz), 4.68 (sextet, 1H, J = 6.1 Hz), 7.20 (m, 3H), 7.45 (m, 1H), 7.54 (m, 1H), 7.75 (m, 1H), 7.85(m, 1H), 8.36(m, 2H).

ESI-MS (m/e) = 388 $(M+H)^+$

Production Example 88



Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methyl-pyridin-3-yl sulphanyl)-N-thiazol-2-yl-benzamide

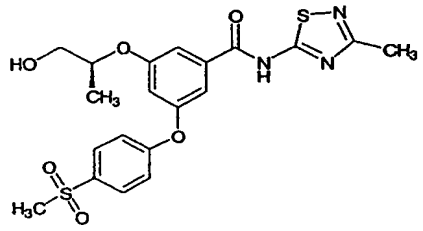
The compound of Production Example 88 was obtained as a white amorphous material by the same method as in Production Example 74, a process in accordance with this, or a combination of these and conventional method using 3-mercapto-6-methyl-pyridine and 3-(2-tert-butyldimethylsiloxy-1-methyl-ethoxy)-5-iodo-N-(thiazol-2-yl)-benzamide obtained using the same method as in Production Example 65 using 3-hydroxy-5-iodo-benzoic acid methyl ester, 1-(tert dimethyl siloxy)-2-hydroxypropane and 2-aminothiazole. Moreover, the removal of tert-butyldimethylsiloxy group which waas a protecting group of hydroxy group was carried out by the same method as in Production Example 2, a process in accordance with this, or a combination of these and

conventional method.

^{1}H-NMR ($CDCl_3$) δ : 1.24 (d, 3H, J = 6.2 Hz), 2.54 (s, 3H), 3.72 (m, 2H), 4.52 (m, 1H), 6.97 (m, 2H), 7.16 (m, 2H), 7.33 (m, 1H), 7.59 (m, 1H), 8.52 (m, 1H), 12.0(br, 1H)

ESI-MS (m/e) = 402 $(M+H)^+$

Production Example 89



Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-(3-methyl-[1,2,4]-thiadiazol-5-yl)-benzamide

4-methanesulphonyl-bromobenzene 33.4 g (142 mmol), palladium acetate 2.67 g (11.9 mmol), 2-(di-tert-butylphosphino) biphenyl 5.31 g (17.8 mmol), potassium phosphate 50.3 g (237 mmol) were added to toluene solution (375 ml) of 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester 25.0 g (119 mmol), and thereafter, reactor was sealed, and thereafter, it was stirred at 130°C for six hours. Ethyl acetate was added to the reaction liquor and it was filtered, and thereafter concentrated under reduced pressure. The obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 2 : 1), and 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester 31.0 g (yield = 69%) was obtained as a white solid.

Trifluoroacetic acid 60 ml was added with ice cooling to methylene chloride solution (100 ml) of the obtained 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester 30.9 g (84.3 mmol), and thereafter the reaction liquor was stirred at room temperature for four hours. The reaction liquor was concentrated under reduced pressure and the obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 1 : 1) and 5-hydroxy-3-(4-methanesulphonyl-phenoxy) benzoic acid methyl ester 15.2 g (yield = 56%) was obtained as a white solid.

(2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane 11.8 g (62.1 mmol) and triphenyl phosphine 16.3 g (62.1 mmol) were added to tetrahydrofuran solution (200 ml) of the obtained 5-hydroxy-3-(4-methanesulphonyl-phenoxy) benzoic acid methyl ester 10.0 g (31.0 mmol), and thereafter, 40 % toluene solution 33.8 ml (77.6 mmol) of diethylazo dicarboxylate was added with ice cooling and the mixture was stirred.at room temperature for 12 hours. The reaction liquor was concentrated under reduced pressure and the obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 8 : 2) and 5-((1S)-2-(tert-butyldimethylsiloxy)-1-methyl-

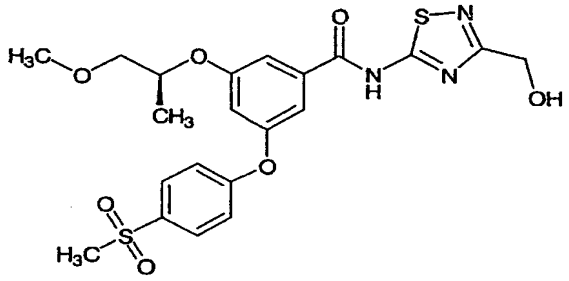
ethoxy)-3-(4-methanesulphonyl-phenoxy)-benzoic acid methyl ester was obtained as a yellow oily substance.

Using the obtained 5-((1S)-2-(t-butyldimethylsiloxy)-1-methyl-ethoxy)-3-(4-methanesulphonyl-phenoxy)-benzoic acid methyl ester 200 mg (0.40 mmol) and 5-amino-3-methyl-[1,2,4] thiadiazole, the compound of Production Example 89 was obtained as a colourless amorphous material using the same method as in Production Example 2, a process in accordance with this, or a combination of these and conventional method.

^{1}H-NMR (CD_3OD) δ: 1.30 (d, 6H, J = 6.2 Hz), 2.50 (s, 3H), 3.12 (s, 3H), 3.68 (d, 2H, J = 5.0 Hz), 4.58-4.63 (m, 1H), 7.01 (s, 1H), 7.23 (d, 2H, J = 8.8 Hz), 7.36 (s, 1H), 7.54 (s, 1H), 7.97 (d, 2H, J = 8.8 Hz).

ESI-MS (m/e) = 464 $(M+H)^+$

Production Example 90



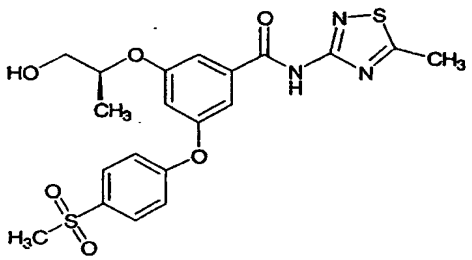
Preparation of N-[3-hydroxymethyl-1,2,4-thiadiazol-5-yl]-3-(4-methanesulphonyl phenoxy)-5-(2-methoxy-1-methyl-ethoxy) benzamide

The compound of Production Example 90 was obtained as a colourless amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89, (2R)-1-methoxy-2-propanol and 5-amino-3-(t-butyldimethylsiloxy methyl)-[1,2,4] thiadiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.34 (3H, d, J = 6.3 Hz), 3.09 (3H, s), 3.41 (3H, s), 3.49-3.64 (2H, m), 4.60-4.72 (1H, m), 4.79 (2H, s), 6.92 (1H, t, J = 2.0 Hz), 7.16 (2H, d, J = 8.7 Hz), 7.43 (1H, br), 7.93 (2H, d, J = 8.7 Hz)

ESI-MS (m/e) = 494 $(M+H)^+$

Production Example 91



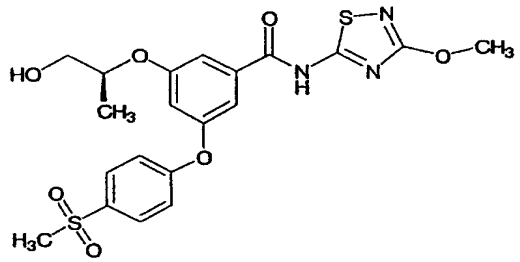
Preparation of 5-(3-hydroxy-1-methyl ethoxy)-3-(4-methanesulphonyl phenoxy)-N-[5-methyl-1,2,4-thiadiazol-3-yl] benzamide

The compound of Production Example 91 was obtained as white solid using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 3-amino-5-methyl-[1,2,4] thiadiazole.

^{1}H-NMR ($CDCl_3$) δ :1.29 (d, 3H, J = 6.3 Hz), 2.76 (s, 3H), 3.07 (s, 3H), 3.79 (m, 2H), 4.57 (m, 1H), 6.81 (m, 1H), 7.12 (d, 2H, J = 8.8 Hz), 7.17 (m, 1H), 7.33(mIH), 7.91 (d, 2H, J = 8.8 Hz), 9.27 (m, 1H).

ESI-MS (m/e) = 464 $(M+H)^+$

Production Example 92



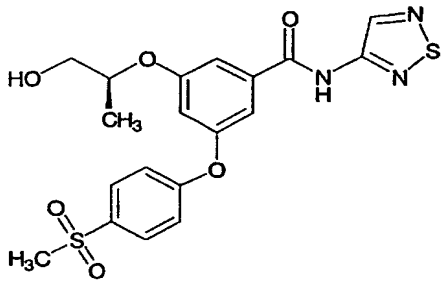
Preparation of 5-(hydroxy-1-methyl ethoxy)-3-(4-methanesulphonyl phenoxy)-N-(3-methoxy-1,2,4-thiadiazol-5-yl) benzamide

The compound of Production Example 92 was obtained as a white amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained by Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 5-amino-3-methoxy-[1,2,4] thiadiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.32 (d, 3H, J = 6.3 Hz), 3.12 (s, 3H), 3.80 (d, 2H, J = 5.5 Hz), 3.99 (s, 3H), 4.61 (m, 1H), 6.87(m, 1H), 7.17 (d, 2H, J = 8.8 Hz), 7.23 (m, 1H), 7.35 (m, 1H), 7.96 (d, 2H, J = 8.8 Hz), 11,2(br, 1H).

ESI-MS (m/e) = 480 $(M+H)^+$

Production Example 93



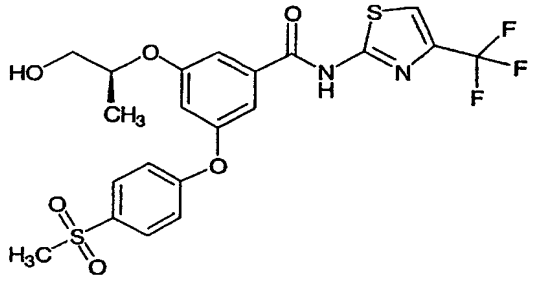
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-(1,2,5-thiadiazol-3-yl) benzamide

The compound of Production Example 93 was obtained as straw-coloured amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained by Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 3-amino-[1,2,5] thiadiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.34 (d, 3H, J = 6.3 Hz), 1.91 (t, 1H, J = 5.7 Hz), 3.09 (s, 3H), 3.80 (m, 2H), 4.60 (m, 1H), 6.89 (m, 1H), 7.17 (d, 2H), 7.18 (m, 1H), 7.35 (m, 1H), 7.96 (d, 2H, J = 8.8 Hz), 8.92 (m, 1H), 9.32 (s, 1H).

ESI-MS (m/e) = 450 $(M+H)^+$

Production Example 94



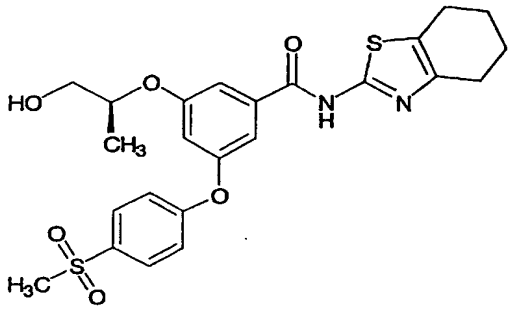
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-(4-trifluoromethyl-thiazol-2-yl) benzamide

The compound of Production Example 94 was obtained as a colourless amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 2-amino-4-trifluoromethyl-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.32 (d, 3H, J = 6.2 Hz), 3.11 (s, 3H), 3.78 (d, 2H, J = 5.1 Hz), 4.57-4.63 (m,

1H), 6.91 (s, 1H), 7.16-7.17 (m, 1H), 7.17 (d, 2H, J = 8.8 Hz), 7.34-7.36 (m, 1H), 7.44-7.46 (m, 1H), 7,96 (d, 2H, J = 8.8 Hz).
ESI-MS (m/e) = 517 $(M+H)^+$

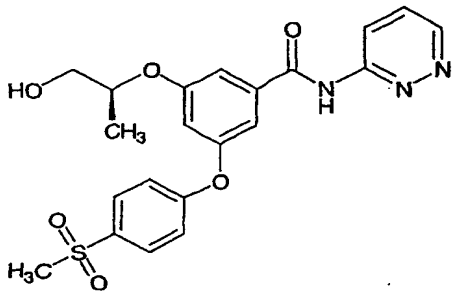
Production Example 95



Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-(4,5,6,7-tetrahydrobenzo thiazol-2-yl) benzamide

The compound of Production Example 95 was obtained as a colourless oily substance using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 2-amino-4,5,6,7-tetrahydrobenzo thiazole.
^{1}H-NMR ($CDCl_3$) δ : 1.26-1.29 (m, 3H), 1.82-1.86 (m, 4H), 2.57-2.72 (m, 4H), 3.09 (s, 3H), 3.73-3.78 (m, 2H), 4.54-4.56 (m, 1H), 6.78-6.81 (m, 1H), 7.09-7.14 (m, 3H), 7.22-7.29 (m, 1H), 7.90-7.95(m, 2H).
ESI-MS (m/e) = 503 $(M+H)^+$

Production Example 96



Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-(pyridazin-3-yl)-benzamide

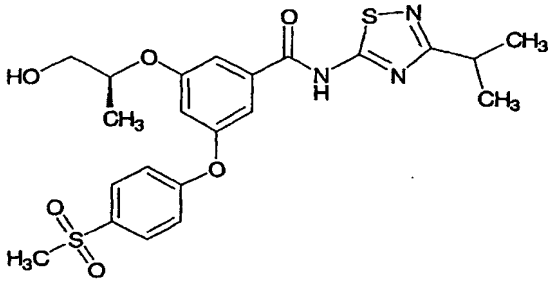
The compound of Production Example 96 was obtained as a colourless amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-

methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 3-amino-pyridazine.

^{1}H-NMR ($CDCl_3$) δ : 1.30 (d, 3H, J = 5.9 Hz), 2.55 (brs, 1H), 3.07 (s, 3H), 3.76 (m, 2H), 4.59 (qt, 1H, J = 5.9, 5.5 Hz), 6.83 (s, 1H), 7.11(d, 2H, J=8.4H $), 7.24(S, 1H), 7.39(S, 1H), 7.52 (dd, 1H, 9.2, J = 4.8 Hz), 7.90 (d, 2H, J = 8.4 Hz), 8.55 (d, 1H, J = 9.2 Hz), 8.93 (m, 1H), 9.54 (brs, 1H).

ESI-MS (m/e) = 444 $(M+H)^+$, 442 $(M-H)^-$

Production Example 97



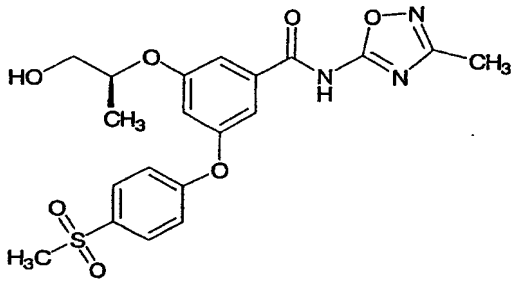
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-N-(3-isopropyl-[1,2,4]-triazol-5-yl)-3-(4-methanesulphonyl phenoxy) benzamide

The compound of Production Example 97 was obtained as a colourless amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 5-amino-3-isopropyl-[1,2,4] triazole.

^{1}H-NMR ($CDCl_3$) δ : 1.33 (d, 6H, J = 7.3 Hz), 1.35 (q, 6H, J = 7.0 Hz), 3.10 (s, 3H), 3.16-3.21 (m, 1H)'3-77-3-79 (m'2H), 4.57-4.62 (m, 1H), 6.91 (s, 1H), 7.16 (d, 2H, J = 8.9 Hz), 7.17 (d, 1H, J = 1.7 Hz), 7.35 (d, 1H, J = 1.7 Hz), 7.95 (d, 2H, J = 8.9 Hz)

ESI-MS (m/e) = 492 $(M+H)^+$

Production Example 98



Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-(3-methyl-[1,2,4] one oxadiazol-5-yl) benzamide

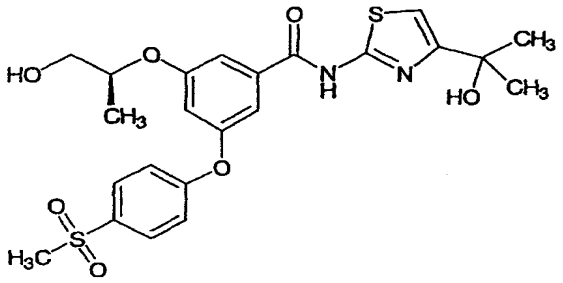
The compound of Production Example 98 was obtained as a colourless amorphous material using

the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 5-amino-3-methyl-[1,2,4] oxadiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.28 (d, 3H, J = 5.9 Hz), 2.31 (s, 3H), 3108 (S'3H), 3.75-3.76 (in, 2H), 4.57-4.58 (m, 1H), 5.60 (brs, 1H), 6.84 (s, 1H), 7.09 (d, 2H, J = 8.6 Hz), 7.24 (s, 1H), 7.35 (s, 1H), 7.87 (d, 2H, J = 8.6 Hz), 10.52 (brs, 1H).

ESI-MS (m/e) = 448 $(M+H)^+$, 446 $(M-H)^-$

Production Example 99



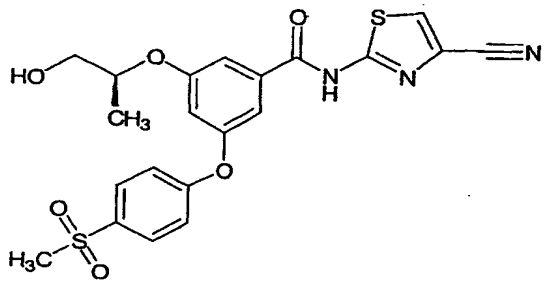
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-N-[4-(1-hydroxy-1-methyl-ethyl)-thiazol-2-yl]-3-(4-methanesulphonyl phenoxy) benzamide

The compound of Production Example 99 was obtained as white solid using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 2-amino-4-(1-hydroxy-1-methyl-ethyl)-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.33 (3H, d, J = 6.2 Hz), 1.61 (6H, s), 3.08 (3H, s), 3.75-3.84 (2H, m), 4.55-4.65 (1H, m), 6.77 (1H, s), 6.88 (1H, t, J = 2.0 Hz), 7.16 (2H, d, J = 8.7 Hz), 7.28 (1H, br), 7.45 (1H, br), 7.95 (2H, d, J = 8.7 Hz)

ESI-MS (m/e) = 507 $(M+H)^+$

Production Example 100



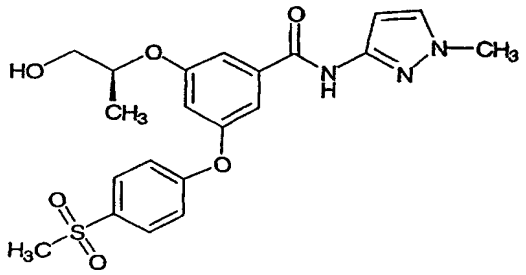
Preparation of N-(4-cyano-thiazol-2-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy) benzamide

The compound of Production Example 100 was obtained as a colourless amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 2-amino-4-cyano-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.32 (d, 3H, J = 6.2 Hz), 2.48 (brs, 1H), 3.12 (s, 3H), 3.75-3.85 (m, 2H), 4.59-4.62 (m, 1H), 6.88 (s, 1H), 7.15 (d, 2H, J = 8.8 Hz), 7.22 (s, 1H), 7.38 (s, 1H), 7.70 (s, 1H), 7.94 (d, 2H, J = 8.8 Hz), 10.52 (brs, 1H).

ESI-MS (m/e) = 474 $(M+H)^+$, 472 $(M-H)^-$

Production Example 101



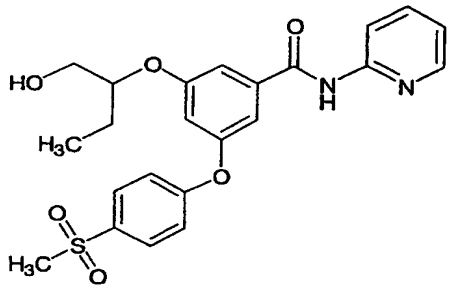
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 101 was obtained as white crystal using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ :1.31 (d, 3H, J = 6.3 Hz), 3.08 (s, 3H), 3.77 (m, 2H), 3.81 (s, 3H), 4.57 (m, 1H), 6.78 (m, 1H), 6.82 (m, 1H), 7.11 (m, 1H), 7.15 (d, 2H, J = 8.9 Hz), 7.30 (m, 2H), 7.93 (d, 2H, J = 8.9 Hz), 8.45 (m, 1H).

ESI-MS (m/e) = 466 $(M+H)^+$

Production Example 102



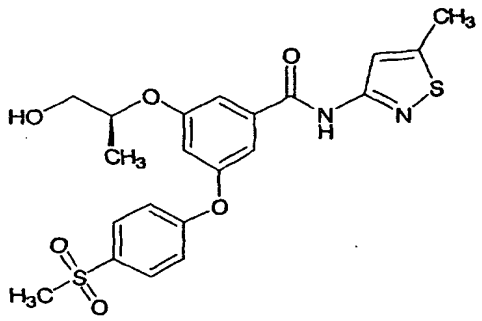
Preparation of 5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonyl phenoxy)-N-(pyridin-2-yl) benzamide

The compound of Production Example 102 was obtained as a colourless amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using (2R)-1-(tert-butyldimethylsiloxy)-2-hydroxy butane and 2-amino-pyridine used instead of 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89 and (2R)-1-(tert-butyldimethylsiloxy)-2-hydroxypropane.

^{1}H-NMR ($CDCl_3$) δ : 1.01 (t, 3H, J = 7.7 Hz), 1.76 (qd, 2H, J = 7.7, 6.2 Hz), 2.10 (brs, 1H), 3.09 (s, 3H), 3.78-3.88 (m, 2H), 4.38-4.44 (m, 1H), 6.86 (s, 1H), 7.10 (dd, 1H, J = 4.0, 8.4 Hz), 7.15 (d, 2H, J = 9.2Hz) 7.17 (s, 1H), 7.37 (s, 1H), 7.77 (dd, 1H, J = 8.4,8-4 Hz), 7.93 (d, 2H, J = 9.2 Hz), 8.29 (d, 1H, J = 4.0 Hz), 8.34 (d, 1H, J = 8.4 Hz), 8.62 (brs, 1H).

ESI-MS(m/e);457 $(M+H)^+$

Production Example 103



Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-(5-methyl-iso thiazol-3-yl) benzamide

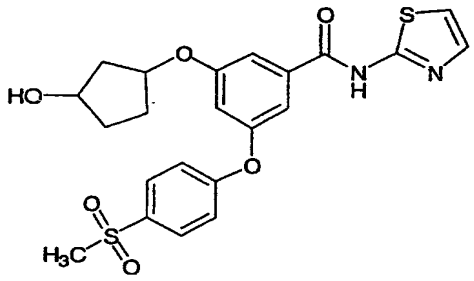
The compound of Production Example 103 was obtained as a white amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-

hydroxypropane and 3-amino-5-methyl-iso thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.30 (d, 3H, J = 6.2 Hz), 2.58 (s, 3H), 3.07 (s, 3H), 3.75 (m, 2H), 4.57 (m, 1H), 6.82 (m, 1H), 7.13 (d, 2H, J = 8.9 Hz), 7.15 (m, 1H), 7.31 (m, 1H), 7.73 (m, 1H), 7.92 (d, 2H, J = 8.9 Hz), 9.12 (m, 1H).

ESI-MS (m/e) = 463 $(M+H)^+$

Production Example 104



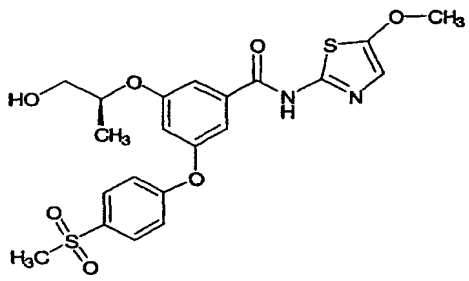
Preparation of 5-(3-hydroxy-cyclopentyl oxy)-3-(4-methanesulphonyl phenoxy)-N-(thiazol-2-yl) benzamide

The compound of Production Example 104 was obtained as a colourless amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(tert-butyl diphenyl siloxy) cyclopentanol and 2-amino-thiazole instead of (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89,.

^{1}H-NMR ($CDCl_3$) δ : 1.92 (m, 6H), 3.08 (s, 3H), 4.39 (s, 1H), 4.82-4.84 (s, 1H), 6.82 (t, 1H, J = 1.9 Hz), 7.00 (d, 1H, J = 3.6 Hz), 7.13 (d, 2H, J = 8.6 Hz), 7.16 (d, 1H, J = 1.9 Hz), 7.23 (d, 1H, J = 3.6 Hz), 7.34 (d, 1H, J=1.9 Hz), 7.92 (d, 2H, J = 8.6 Hz)

ESI-MS (m/e) = 475 $(M+H)^+$

Production Example 105



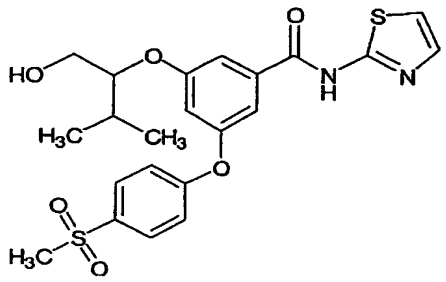
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-(5-methoxy-thiazol-2-yl) benzamide

The compound of Production Example 105 was obtained as white solid using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89, (2R)-1-(t-butyl dimethylsiloxy)-2-hydroxypropane and 2-amino-5-methoxy-thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.28 (d, 3H, J = 6.2 Hz), 3.07 (s, 3H), 3.75 (d, 2H, J = 5.6 Hz), 3.87 (s, 3H), 4.57 (m, 1H), 6.52 (s, 1H), 6.81 (m, 1H), 7.12 (d, 2H, J = 8.8 Hz), 7.17 (m, 1H), 7.31 (m, 1H), 7.90 (d, 2H, J = 8.8 Hz), 11.5(br, 1H)

ESI-MS (m/e) = 479 $(M+H)^+$

Production Example 106



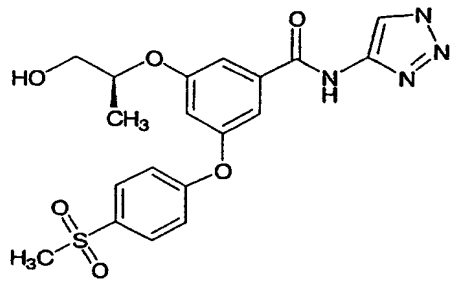
Preparation of 5-(1-hydroxymethyl-2-methyl-propoxy)-3-(4-methanesulphonyl phenoxy)-N-(thiazol-2-yl) benzamide

The compound of Production Example 106 was obtained as a white amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 1-(tert-butyldimethylsiloxy)-3-methyl-butane-2-ol and 2-amino-thiazole instead of (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89.

^{1}H-NMR ($CDCl_3$) δ : 0.97 (m, 6H), 2.05 (m, 1H), 3.07 (s, 3H), 3.83 (m, 2H), 4.22 (m, 1H), 6.84 (m, 1H), 6.96 (d, 1H, J = 3.7 Hz), 7.11 (d, 2H, J = 8.9 Hz), 7.18 (m, 1H), 7,23 (d, 1H, J, 3,7 Hz), 7.39 (m, 1H), 7.91 (d, 2H, J = 8.8 Hz), 12.0(br, 1H).

ESI-MS (m/e) = 477 $(M+H)^+$

Production Example 107



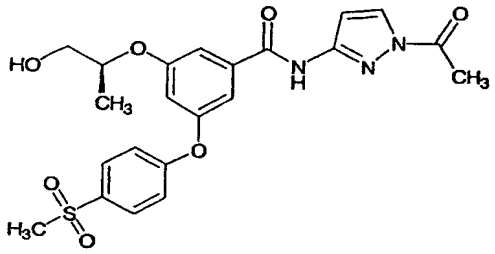
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-(1H-[1,2,3] triazol-4-yl) benzamide

The compound of Production Example 107 was obtained as a colourless amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 4-amino-1H-[1,2,3] triazole.

^{1}H-NMR ($CDCl_3$) δ : 1.31 (d, 3H, J = 6.2 Hz), 3.11 (s, 3H), 3.34 (s, 1H), 3.67-3.68 (m, 2H), 4.56-4.60 (m, 2H), 6.93 (s, 1H), 7.21 (d, 2H, J = 8.8 Hz), 7.25 (s, 1H), 7.43 (s, 1H), 7.94 (d, 2H, J = 8.8 Hz), 8.08 (brs, 1H).

ESI-MS (m/e) = 433 $(M+H)^+$, 431 $(M-H)^-$

Production Example 108



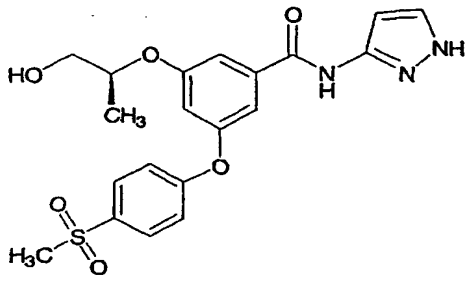
Preparation of N-(1-acetyl-1H-pyrazol-3-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy) benzamide

The compound of Production Example 108 was obtained as a white amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 3-amino-1-acetyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 1.36 (d, 3H, J = 6.3 Hz), 2.65 (s, 3H), 3.12 (s, 3H), 3.82 (m, 2H), 4.61 (m, 1H), 6.89 (m, 1H), 7.16-7.22 (m, 4H), 7.35 (m, 1H), 7.98 (d, 2H, J = 8.8 Hz), 8.22 (d, 1H, J =

3.OHZ), 8.46 (br, 1H).
ESI-MS (m/e) = 474 $(M+H)^+$

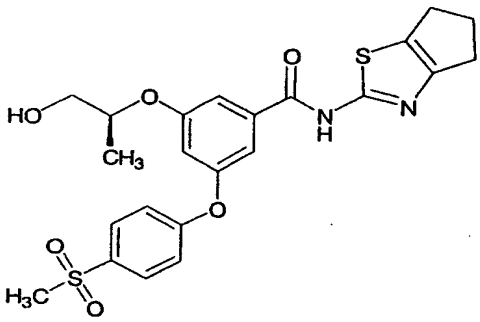
Production Example 109



Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-(pyrazol-3-yl) benzamide

The compound of Production Example 109 was obtained as a white amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 3-amino-pyrazole.
^{1}H-NMR ($CDCl_3$) δ : 1.26 (d, 3H, J = 6.3 Hz), 3.05 (s, 3H), 3.73 (m, 2H), 4.52 (m, 1H), 6.75 (m, 2H), 7.06 (d, 2H, J = 8,8H1), 7.14 (m, 1H), 7.32 (m, 1H), 7.46 (m, 1H), 7.85 (d, 2H, J = 8.8 Hz), 9.72 (m, 1H).
ESI-MS (m/e) = 432 $(M+H)^+$

Production Example 110

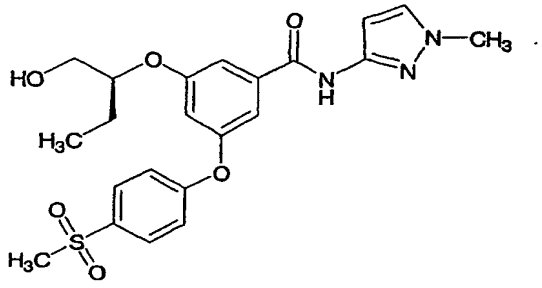


Preparation of N-(5,6-dihydro-4H-cyclopenta thiazol-2-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy) benzamide

The compound of Production Example 110 was obtained as a colourless amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-

methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 2-amino-5,6-dihydro-4H-cyclopentane thiazole.
^{1}H-NMR ($CDCl_3$) δ : 1.28 (d, 3H, J=6.2Hz), 2.44 (tt, 2H, J = 7.0, 7.0 Hz), 2.61 (t, 2H, J = 7.0 Hz), 2.90 (t, 2H, J = 7.0 Hz), 3.08 (s, 3H), 3.70-3.76 (m, 2H), 4.51-4.55 (m, 1H), 6.76 (s, 1H), 7.10 (d, 2H, J = 8.8 Hz), 7.12 (s, 1H), 7.28 (s, 1H), 7.90 (d, 2H, J = 9.2 Hz)
ESI-MS (m/e) = 489 $(M+H)^+$, 487 $[M-H]^-$

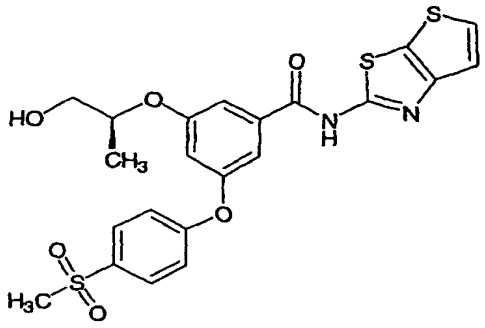
Production Example 111



Preparation of 5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonyl phenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Preparation Example 111 was obtained as a white amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using (2R)-1-(tert-butyldimethylsiloxy) -butane-2-ol and 3-amino-1-methyl-1H-pyrazole instead of 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89 and (2R)-1-(tert-butyldimethylsiloxy)-2-hydroxypropane.
^{1}H-NMR ($CDCl_3$) δ = 0.93 (t, 3H, J = 7.5 Hz), 1.69 (quintet, 1H, J = 7.5 Hz), 2.75 (t, 1H, J = 6.2 Hz), 3.06 (s'3H), 3.74 (s, 3H), 3.70-3.80 (m, 2H), 4.33 (m, 1H), 6.77 (m, 2H), 7.09 (d, 2H, J = 8.8 Hz), 7.11 (m, 1H), 7.27 (m, 2H), 7.99 (d, 2H, J = 8.8 Hz), 9.03 (m, 1H).
ESI-MS (m/e) = 460 $(M+H)^+$

Production Example 112



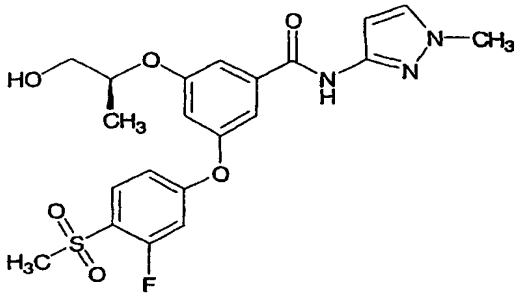
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-(thieno [3,2-d] thiazol-2-yl) benzamide

The compound of Production Example 112 was obtained as a colourless amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 2-amino-thieno [3,2-d] thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.30 (d, 3H, J = 6.2H), 2.05 (brs, 1H), 3.09 (s, 3H), 3.76-3.78 (m, 2H), 4.55-4.57 (m, 1H), 6.84 (s, 1H), 7.11 (d, 2H, J = 8.8 Hz), 7.11 (s, 1H), 7.19 (s, 1H), 7.36 (s, 1H), 7.38 (s, 1H), 7.92 (d, 2H, J=8.8Hz), 10.42 (brs, 1H).

ESI-MS (m/e) = 505 $(M+H)^+$, 503 $(M-H)^-$

Production Example 113



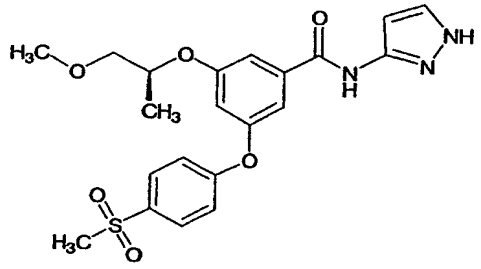
Preparation of 3-(3-fluoro-4-methanesulphonyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 113 was obtained as white crystal using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(3-fluoro-4-methanesulphonyl phenoxy)-5-hydroxy-benzoic acid methyl ester obtained using the same process as in Production Example 42, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 1.31 (d, 3H, J = 6.3 Hz), 2.20 (t, 1H, J = 6.5Hl), 3.23 (s, 3H), 3.77 (m, 2H),

3.80 (s, 3H), 4.57 (sextet, 1H, J = 4.5 Hz), 6.79-6.93 (m, 4H), 7.14 (m, 1H), 7.30 (m, 1H), 7.33 (m, 1H), 7,92 (t, 1H, J = 8.4 Hz), 8.57 (br, 1H).
ESI-MS (m/e) = 464 $(M+H)^+$

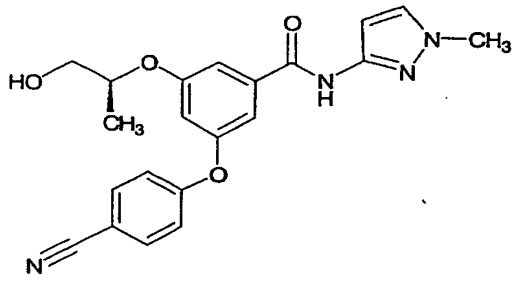
Production Example 114



Preparation of 3-(4-methanesulphonyl phenoxy)-5-(2-methoxy-1-methyl-ethoxy)-N-(pyrazol-3-yl) benzamide

The compound of Production Example 114 was obtained as a white amorphous substance using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained in Production Example 89, (2R)-1-methoxy-2-propanol and 3-amino-pyrazole.
^{1}H-NMR ($CDCl_3$) δ : 1.32 (d, 3H, J = 6.2 Hz), 3.05 (s, 3H), 3.39 (s, 3H), 3.50-3.60 (m, 2H), 4.60 (m, 1H), 6.80 (t, 1H, JE2.2 Hz), 6.85 (d, 1H, J= 2.2 Hz), 7.09 (d, 2H, J = 8.8 Hz), 7.16 (s,t, 1H, J = 2.2 Hz), 7.39 (t, 1H, J = 2.2 Hz), 7.47 (d, 1H, J = 2.2 Hz), 7.87 (d, 2H, J = 8.8 Hz), 9.80 (br, 1H).
ESI-MS (m/e) = 446 $(M+H)^+$

Production Example 115



Preparation of 3-(4-cyano-phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

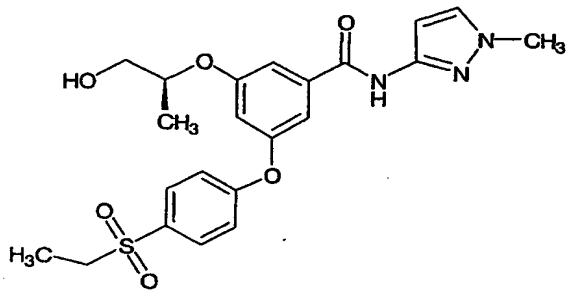
The compound of Production Example 115 was obtained as a colourless amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using (2R)-1-(t-butyldimethylsiloxy)-2-

hydroxypropane, 3-amino-1-methyl-1H-pyrazole and 3-(4-cyano-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained by same process as in Production Example 1 using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester and p-cyanophenyl boric acid,.

^{1}H-NMR ($CDCl_3$) δ : 1.30 (d, 3H, J = 6.2 Hz), 2.31 (brs, 1H), 3.76-3.79 (m, 2H), 3.79 (s, 3H), 4.54 (qt, 1H, J = 6/2H2,4-). Hz), 6177 (d, 1H, J = 2.2 Hz), 6.78 (s, 1H), 7.07 (d, 2H, J = 8.8 Hz), 7.09 (s, 1H), 7.27 (s, 1H), 7.28 (d, 1H, J = 2.2 Hz), 7.63 (d, 2H, 8.8 Hz), 8.64 (brs, 1H).

ESI-MS (m/e) = 393 $(M+H)^+$

Production Example 116



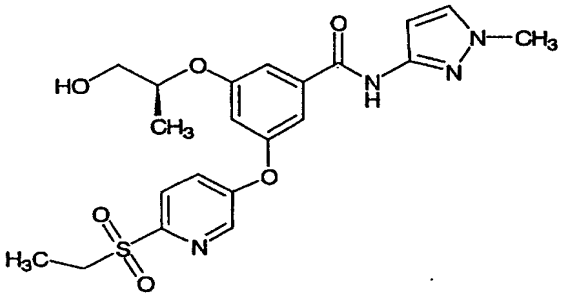
Preparation of 3-(4-ethylsulfonyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 116 was obtained as a colourless amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of such procedures, using (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane, 3-amino-1-methyl-1H-pyrazole and 3-(4-ethylthio-phenoxy)-5-hydroxy-benzoic acid methyl ester obtained by deprotecting methoxy methyl group of 3-(4-ethylthio-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained by the same process as in Production Example 1 using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester and p-ethylthio phenyl boric acid, (,.

^{1}H-NMR ($CDCl_3$) δ : 1.32 (d, 3H, J = 6.2 Hz), 1.33 (t, 3H, J = 7.7 Hz), 2.05 (brs, 1H), 3.14 (q, 2H, J = 7.7 Hz), 3.75-3.79 (m, 2H), 3.81 (s, 3H), 4.56 (qt, 1H, J = 6.2, 3.7 Hz), 6.78 (s, 1H), 6.81 (d, 1H, J = 2.2 Hz), 7.11 (s, 1H), 7.12 (d, 2H, J = 8.8 Hz), 7.28 (d, 1H, J = 2.2 Hz), 7.28 (s, 1H), 7.87 (d, 2H, J = 8.8 Hz), 8.41 (brs, 1H)

ESI-MS(m/e) = 460 $(M+H)^+$, 458 $(M-H)^-$

Production Example 117



Preparation of 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

5-bromo-2-ethane sulfonyl pyridine 178 mg (0.71 mmol) and cesium carbonate 232 mg (0.71 mmol) were added to N,N-dimethylformamide solution (1.0 ml) of 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester 100 mg (0.47 mmol) and thereafter, under a nitrogen atmosphere, it was stirred at 100°C for two hours 30 minutes. Ammonium chloride aqueous solution and ethyl acetate were added to the reaction liquor, aqueous layer was extracted with ethyl acetate and thereafter the organic layer was washed with saturated aqueous sodium chloride solution, and after drying, concentrated under reduced pressure. The obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 1 : 1) and 3-(6-ethane sulfonyl-pyridin-3-yloxy)-5-methoxymethoxy benzoic acid methyl ester 165 mg (yield = 91%) was obtained as a colourless oily substance.

To methylene chloride solution (50.0 ml) of the obtained ester 11.8 g (30.9 mmol), trifluoroacetic acid 30.0 ml were added, and the reaction liquor was stirred at room temperature for five hours. The reaction liquor was concentrated under reduced pressure and the obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 2 : 1) and 3-(6-ethane sulfonyl-pyridin-3-yloxy)-5-hydroxybenzoic acid methyl ester 8.86 g (yield = 85%) were obtained as a colourless oily substance.

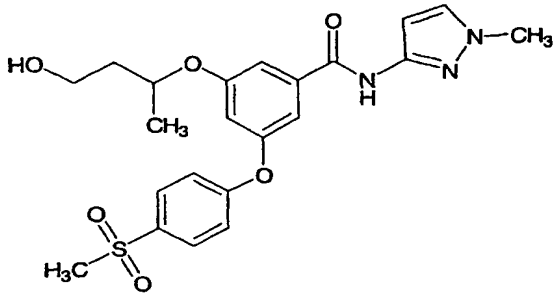
(2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane 1.02 g (5.34 mmol) and triphenyl phosphine 1.40 g (5.34 mmol) were added to tetrahydrofuran solution (30.0 ml) of the obtained phenol body 1.00 g (2.97 mmol), and thereafter, 40 % toluene solution 2.42 ml (5.34 mmol) of diethylazo dicarboxylate was added with ice cooling and the mixture stirred.at room temperature for one hour. The reaction liquor was concentrated under reduced pressure and the obtained residue was refined using silica gel column chromatography (hexane : ethyl acetate = 3 : 2) and 3-((1S)-2-(t-butyldimethylsiloxy)-1-methyl-ethoxy)-5-(6-ethane sulfonyl-pyridin-3-yloxy)-benzoic acid methyl ester 1.31 g (yield = 87%) were obtained as a colourless oily substance.

The compound of Production Example 117 was obtained as a colourless amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using the obtained 3-((1S)-2-(t-butyldimethylsiloxy)-1-methyl-ethoxy)-5-(6-ethane sulfonyl-pyridin-3-yloxy)-benzoic acid methyl ester and 3-amino-1-methylpyrazole.

^{1}H-NMR ($CDCl_3$) δ :1.32 (d, 3H, J = 6.2 Hz), 1.33 (t, 3H, J = 7.3 Hz), 3.40 (q, 2H, J = 7.3 Hz), 3.75-3.77 (m, 2H), 3.81 (s, 3H), 4.54-4.59 (m, 1H, J = 6.2, 1 Hz), 6.76 (d, 1H, J = 2.2 Hz), 6.81 (strange dd, 1H, J = 2.2, 2.2H), 7.14 (α d)1H, J = 2.2, 1.7 Hz), 7.28 (d, 1H, J = 2.2 Hz), 7.32 (s,d, 1H, J = 2.2, 1.7 Hz), 7.43 (dd, 1H, J = 8.8, 2.6 Hz), 8.05 (d, 1H, J = 8.8 Hz), 8.45 (brs, 1H), 8.47 (d, 1H, J = 2.6 Hz).

ESI-MS (m/e) = 461 $(M+H)^+$, 459 $(M-H)^-$

Production Example 118



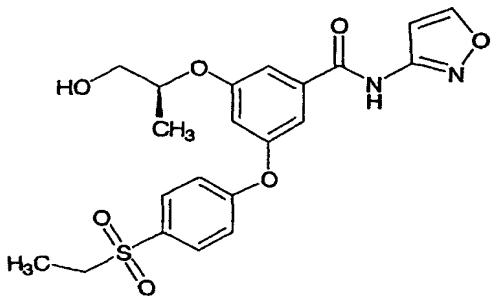
Preparation of 5-(3-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonyl phenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 118 was obtained as a colourless amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained by Production Example 89, 4-(tert-butyldimethylsiloxy)-butane-2-ol and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 1.37 (3H, d, J = 6.2 Hz), 1.88-1.93 (2H, m), 1-96-2.09 (1H, m), 3.08 (3H, s), 3.78-3.87 (2H, m), 3.81 (3H, s), 6.78 (1H, d, J = 2.0 Hz), 6.81 (1H, t, J = 2.1 Hz), 7.11/7-18 (3H, m) 7-29 (1H, d'I= 2-2 Hz), 7.35 (1H, br), 7.92 (2H, d, J = 9.0 Hz), 8.51 (1H, br).

ESI-MS (m/e) = 460 $(M+H)^+$

Production Example 119



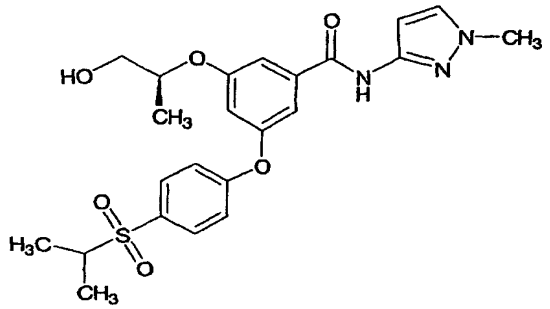
Preparation of 3-(4-ethane sulfonyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl) benzamide

The compound of Production Example 19 was obtained as a colourless amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of such procedures, using (2R)-1-(t-butyldimethylsiloxy)-.2-hydroxypropane, 3-amino-isoxazole and 3-(4-ethylthio-phenoxy)-5-hydroxy-benzoic acid methyl ester obtained by deprotecting the methoxy methyl group of 3-(4-ethylthio-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained by same process as in Production Example 1 using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester and p-ethylthio phenyl boric acid.

^{1}H-NMR ($CDCl_3$) δ : 1.32 (t, 3H, J = 7.4 Hz), 1/32 (d, 3H, J = 6.3 Hz), 3.13 (q, 2H, J = 7.4 Hz), 3.76-3-79 (m, 2H), 4.56-4-62 (m, 1H), 6.87 (t, 1H, J = 1.8 Hz), 7,14 (d, 2H, J = 8.7 Hz), 7.16 (d, 1H, J = 1.8 Hz), 7.26 (d, 1H, J = 1.8 Hz), 7.31 (s, 1H), 7.93 (d, 2H, J = 8.7 Hz), 8.34 (s, 1H).

ESI-MS (m/e) = 477 $(M+H)^+$

Production Example 120



Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-isopropyl sulfonyl phenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

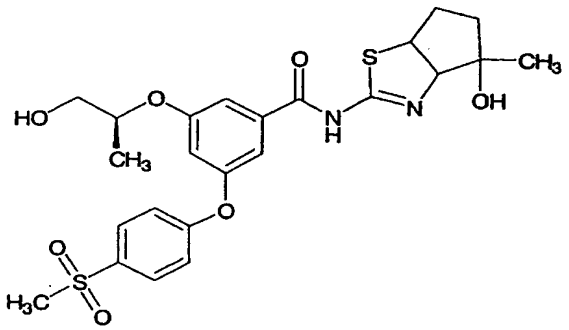
The compound of Production Example 120 was obtained as a colourless amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of such procedures, using (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane, 3-amino-1-methyl-1H-pyrazole and 3-(4-isopropylthio-phenoxy)-5-hydroxy-benzoic acid methyl ester obtained by

deprotecting the methoxy methyl group of 3-(4-isopropylthio-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained by same process as in Production Example 1 using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester and p - isopropylthio phenyl boric acid.

^{1}H-NMR ($CDCl_3$) δ : 1.32 (d, 3H, J = 6.2 Hz), 1.32 (d, 6H, J = 7.0 Hz), 3,20 (septet, 1H, J = 7.0 Hz), 3.76-3.77 (m, 2H), 3.79 (s, 3H), 4.55 (qt, 1H, J = 6.2, 4.0 Hz), 6.79 (d, 1H, J = 2.2 Hz), 6.80 (s, 1H), 7.10 (d, 2H, J = 8.8Hz), 7.13 (s, 1H), 7.29 (d, 1H, J = 2.2 Hz), 7.29 (s, 1H), 7.83 (d, 2H, J = 8.8 Hz), 8.61 (brs, 1H).

ESI-MS (m/e) = 474 $(M+H)^+$, 472 $(M-H)^-$

Production Example 121



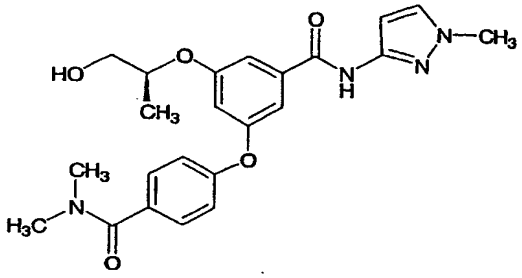
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-N-(4-hydroxy-4-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta thiazol-2-yl)-3-(4-methanesulphonyl phenoxy) benzamide

The compound of Production Example 121 was obtained as a colourless amorphous substance material using the same process as in Production Example 89, a procedure in accordance with this or a combination of such procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained by Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 2-amino-4-hydroxy-4-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta thiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.27-1.33 (3H, m), 1.60 (3H, s), 2.56 (2H, m), 2.75-3.07 (2H, m), 3.08 (3H, s), 3.74-3.82 (2H, m), 4.53-4.65 (1H, m), 6.75-6.83 (1H, m), 7.11-7.20 (3H, m), 7.29-7.35 (1H, m), 7.93 (2H, d, J = 8.9 Hz).

ESI-MS (m/e) = 519 $(M+H)^+$

Production Example 122

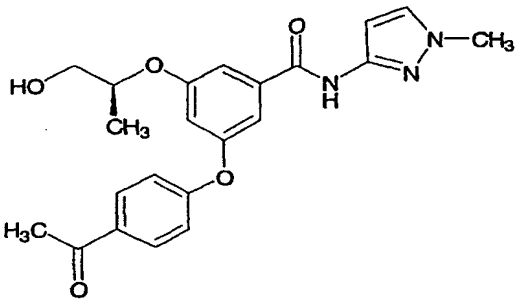


Preparation of 3-(4-dimethylcarbamoyl-phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 122 was obtained as colourless amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane, 3-amino-1-methyl-1H-pyrazole and 3-(4-dimethylcarbamoyl-phenoxy)-5-hydroxy-benzoic acid methyl ester obtained by deprotecting the methoxy methyl group of 3-(4-dimethylcarbamoyl-phenoxy)-5-methoxy-methoxy-benzoic acid methyl ester obtained by converting the formyl group of 3-(4-formyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained by same process as in Production Example 1 from 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester and p-formylphenyl boric acid, to a carboxyl group and thereafter carrying out a condensation reaction with dimethylamine.

^{1}H-NMR ($CDCl_3$) δ : 1.33 (d, 3H, J = 6.2 Hz), 2.11 (brs, 1H), 3.08 (s, 3H), 3.13 (s, 3H), 3.74-3.81 (m, 2H), 3.83 (s, 3H), 4.54-4.58 (m, 1H), 6.77 (s, 1H), 6.80 (s, 1H), 7.06 (d, 2H, J = 7.7 Hz), 7.10 (s, 1H), 7.26 (s, 1H), 7.30 (s, 1H), 7.46 (d, 2H, J = 7.7 Hz), 8.49 (brs, 1H)ES mechanic one MS(m/e) = 439 $(M+H)^+$, 437 $(M-H)^-$

Production Example 123



Preparation of 3-(4-acetyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

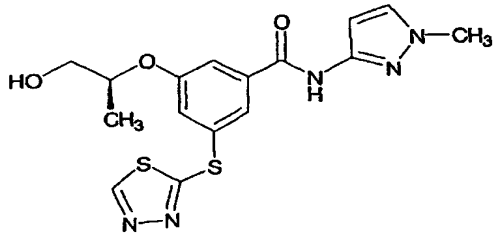
The compound of Production Example 123 was obtained as a colourless amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination

of such procedures, using (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane, 3-amino-1-methyl-1H-pyrazole and 3-(4-acetyl-phenoxy)-5-hydroxy-benzoic acid methyl ester obtained by deprotecting the methoxymethyl group of 3-(4-acetyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained by reacting methyl magnesium bromide with 3-(4-formyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained using the same method as in Production Example 122 and, subjecting to a successive oxidation reaction.

^{1}H-NMR ($CDCl_3$) δ : 1.30 (d, 3H, J = 6.2 Hz), 2.59 (s, 3H), 3.75-3.76 (m, 2H), 3.79 (s, 3H), 4.52-4.56 (m, 1H, JF6.2, -Hz), 6.78 (d, 1H, J = 2.2Hz, dd, 1H, J = 2.2, 1.8 Hz), 7.04 (d, 2H, J= 8.8 Hz), 7.07 (dd, 1H, J = 1.8, 1.8 Hz), 7.25 (dd, 1H, J = 2.2, 1.8 Hz), 7.26 (d, 1H, J = 2.2 Hz), 7.95 (d, 2H, J = 8.8 Hz), 8.52 (brs, 1H).

ESI-MS (m/e) = 410 $[M+H]^+$, 408 $[M-H]^-$

Production Example 124



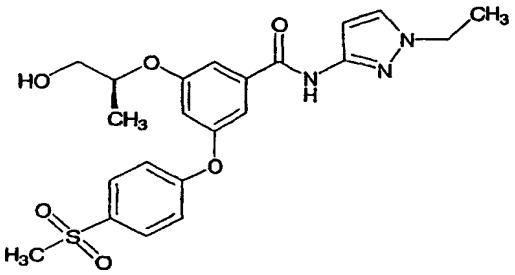
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(1,3,4-thiadiazol-2-yl sulphanyl) benzamide

The compound of Production Example 124 was obtained as a colourless amorphous material using the same procedures as in Production Example 74 or 82, a procedure in accordance with these or a combination of such procedures, using 3-hydroxy-5-iodobenzoic acid methyl ester, 1-tert dimethyl siloxy-2-hydroxypropane, 2-mercapto-[1,3,4] thiadiazole and 3-amino-1-methyl-1H-pyrazole..

^{1}H-NMR ($CDCl_3$) δ : 1.31 (3H, d, J = 6.2 Hz), 3.74-3.79 (2H, m), 3.82 (3H, s), 4.54-4.63 (1H, m), 6.78 (1H, d, J = 2.2 Hz), 7.30 (1H, d, J = 2.3 Hz), 7.39 (1H, m), 7.54 (1H, m), 7.69 (1H, m), 8.55 (1H, br), 9.05 (1H, s).

ESI-MS (m/e) = 392 $(M+H)^+$

Production Example 125



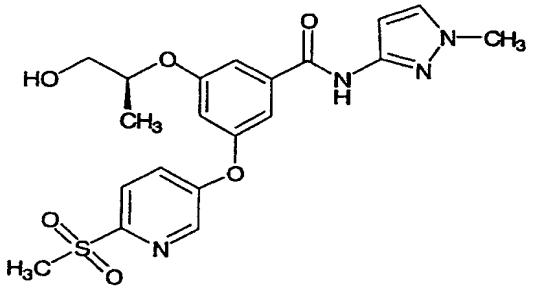
Preparation of N-(1-ethyl-1H-pyrazol-3-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenoxy) benzamide

The compound of Production Example 125 was obtained as a white amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained by Production Example 89, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 3-amino-1-ethyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 1.30 (d, 3H, J = 6.2 Hz), 1.43 (plain), 3.07 (s, 3H), 3.76 (m, 2H), 4.05 (q, 2H, J = 7.3 Hz), 4.56 (m, 1H), 6.79 (m, 2H), 7.12 (d, 2H, J = 8.8 Hz), 7.14 (m, 1H), 7.30 (m, 1H), 7.33 (m, 1H), 7.92 (d, 2H, J = 8.8 Hz), 8.70 (m, 1H).

ESI-MS (m/e) = 460 $(M+H)^+$

Production Example 126



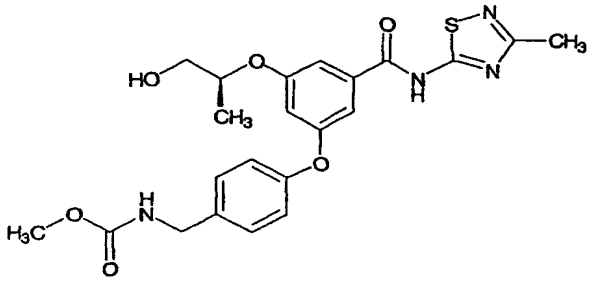
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methanesulphonyl pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 126 was obtained as a white amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-methanesulphonyl pyridine, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 1.29 (d, 3H, J = 6.3 Hz), 3.22 (s, 3H), 3.75(m32H), 3.78 (s, 3H), 4.55 (m,

1H), 6.75 (m, 1H), 6.78 (m, 1H), 7.11 (m, 1H), 7.26 (m, 1H), 7.29 (m, 1H), 7.42 (dd, 1H, J = 2.9, 8.5 Hz), 8.03 (d, 1H, J = 8.5 Hz), 8.44 (d, 1H, J = 2.9 Hz), 8.65 (m, 1H).
ESI-MS (m/e) = 447 $(M+H)^+$

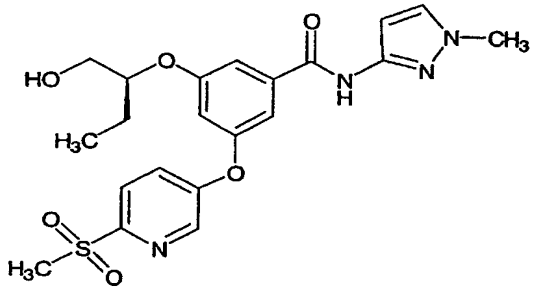
Production Example 127



Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methoxycarbonylamino methyl-phenoxy)-N-(3-methyl-1,2,4-thiadiazol-5-yl) benzamide

Compound of Production Example 127 was obtained as a colourless amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane, 5-amino-3-methyl-[1,2,4] - thiadiazole, and 3-(4-methoxycarbonylamino methylphenoxy)-5-hydroxy-benzoic acid methyl ester obtained by deprotecting the methoxy methyl group of 3-(4-methoxycarbonylamino methylphenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained using the same method as in Production Example 59 using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester instead of 5-hydroxy-3-isopropoxy benzoic acid methyl ester.
^{1}H-NMR ($CDCl_3$) δ : 1.29 (d, 3H, J = 6.2 Hz), 2.45 (s, 3H), 3.71 (s, 3H), 3.73-3.78 (m, 2H), 4.35 (d, 2H, J = 6.2 Hz), 4.50-4.57 (m, 1H, J = 6.2Hz,-), 5.08 (brs, 1H), 6.76 (s, 1H), 6.97 (d, 2H, J = 8.3 Hz), 7.01 (s, 1H), 7.16 (s, 1H), 7.27 (d, 2H, J = 8.3 Hz), 10.8(brs, 1H).
ESI... MS(m/e) = 495 $(M+Na)^+$, 473 $(M+H)^+$, 471 $(M-H)^-$

Production Example 128



Preparation of 5-(1-hydroxymethyl-propoxy)-3-(6-methanesulphonyl pyridin-3-yloxy)-N-(1-

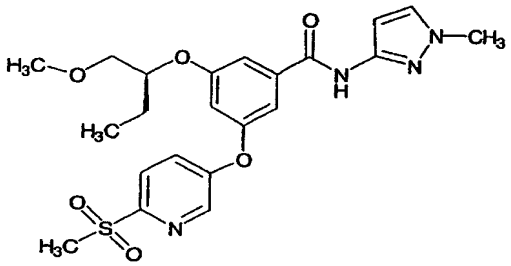
methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 128 was obtained as a colourless amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-methanesulphonyl pyridine, (2S)-1-(tert-butyldimethylsiloxy)-2-hydroxy butane and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 0.99 (t, 3H, J = 7.5 Hz), 1.70-1.77 (m, 2H), 3.24 (s, 3H), 3.79-3.82 (m, 5H), 4.36-4.40 (m, 1H), 6.78 (d, 1H, J = 1.8 Hz), 6.85 (d, 1H, J = 1.8 Hz), 7.13 (s, 1H), 7.29 (d, 1H, J = 2.3 Hz), 7.34 (d, 1H, J = 2.3 Hz), 7.46 (dd, 1H, J = 2.6, 8.9 Hz), 8.08 (d, 1H, J = 8.9 Hz), 8.48 (d, 1H, J = 2.6 Hz).

ESI-MS (m/e) = 461 $(M+H)^+$

Production Example 129



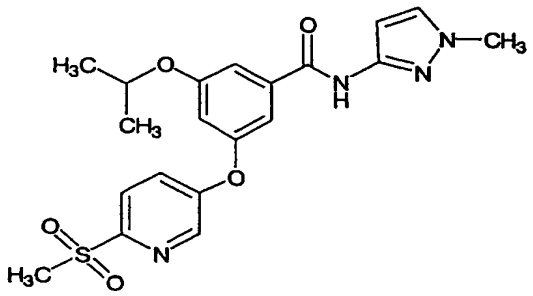
Preparation of 3-(6-methanesulphonyl pyridin-3-yloxy)-5-(1-methoxymethyl-propoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 129 was obtained as a colourless amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-methanesulphonyl pyridine, (2S)-1-methoxy-2-hydroxy butane and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 0.99 (t, 3H, J = 7.4 Hz), 1.74-1.79 (m, 2H), 3.24 (s, 3H), 3.37 (s, 3H), 3.56-3.57 (m, 2H), 3.79 (s, 3H), 4.37-4.40 (m, 1H), 6.79 (s, 1H), 6.87 (t, 1H, J = 1.2 Hz), 7.14 (s, 1H), 7.29 (d, 1H, J = 1.2 Hz), 7.34 (d, 1H, J = 1.2 Hz), 7.45 (dd, 1H, J = 2.0, 8.6 Hz), 8.06 (d, 1H, J = 8.6 Hz), 8.48 (d, 1H, J = 2.0 Hz)

ESI-MS (m/e) = 475 $(M+H)^+$

Production Example 130



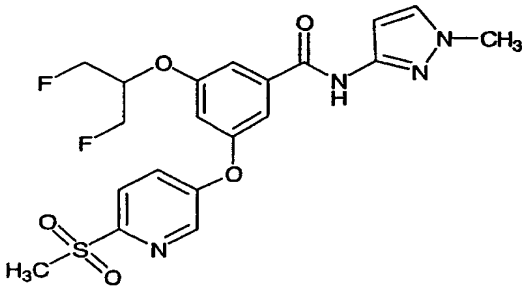
Preparation of 5-isopropoxy-3-(6-methanesulphonyl pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 130 was obtained as a white amorphous material using the same process as in Production Example 130, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-methanesulphonyl pyridine, 2-hydroxypropane and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 1.35 (d, 6H, J = 6.2 Hz), 3.22 (s, 3H), 3.77 (s, 3H), 6.75 (septe, 1H, J = 6.2 Hz), 6.74 (m, 1H), 6.76 (m, 1H), 7.08 (m, 1H), 7.24 (m, 1H), 7.26 (m, 1H), 7.41 (dd, 1H, J = 2.9, 8.8 Hz), 8.03 (d, 1H, J = 8.8 Hz), 8.44 (d, 1H, J = 2.9 Hz), 8.64 (m, 1H).

ESI-MS (m/e) = 431 $(M+H)^+$

Production Example 131



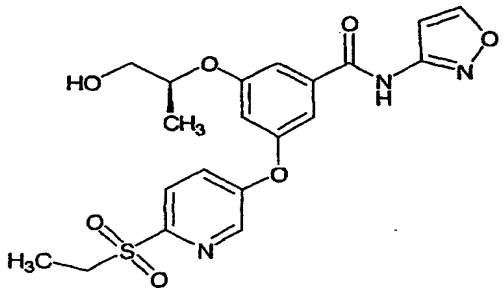
Preparation of 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonyl pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 131 was obtained as a white amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-methanesulphonyl pyridine, 1,3-difluoro-2-propanol and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 3.23 (s, 3H), 3.75 (s, 3H), 4.55-4.61 (m, 2H), 4.61-4.80 (m, 3H), 6.75 (m,

1H), 6.88 (m, 1H), 7.18 (m, 1H), 7.27 (m, 1H), 7.34 (m, 1H), 7.43 (dd, 1H, J = 2.4, 8.4 Hz), 8.04 (d, 1H), 8144 (d, 1H, J = 2.4 Hz), 8.84 (br, 1H).
ESI-MS (m/e) = 467 $(M+H)^+$

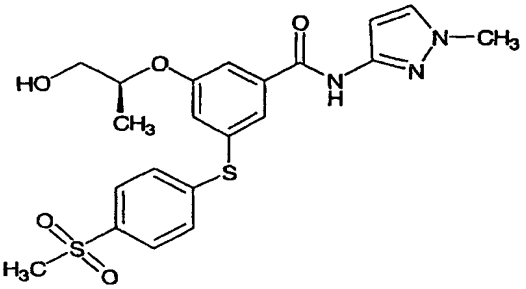
Production Example 132



Preparation of 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl) benzamide

The compound of Production Example 132 was obtained as a colourless amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-ethane sulfonyl pyridine, (2R)-1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 3-amino-isoxazole.
^{1}H-NMR ($CDCl_3$) δ = 1.31 (d, 3H, J = 6.2 Hz), 1-32 (t, 3H, J = 7.3 Hz), 2.22 (brs, 1H), 3.40 (q, 2H, J = 7.3 Hz), 3.75-3.77 (m, 2H), 6.2, -Hz) 4.56-4.61 (m, 1H), 6.86 (d, 1H, J = 2.2 Hz), 7.17 (d, 1H, J = 2.2 Hz), 7.26 (d, 1H, 0.7 Hz), 7.40 (d, 1H, J = 2.2 Hz), 7.43 (dd, 1H, J = 8.8, 2.9 Hz), 8.04 (d, 1H, J = 8.8 Hz), 8.26 (d, 1H, J = 0.7 Hz), 8.46 (d, 1H, J = 2.9 Hz), 9.83 (brs, 1H).
ESI-MS (m/e) = 448 $(M+H)^+$, 446 $(M-H)^-$

Production Example 133



Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenyl sulphanyl)-N-(1-

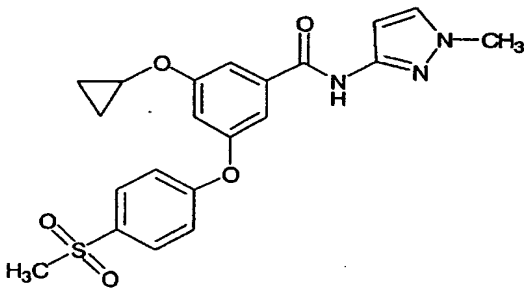
methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 133 was obtained as a colourless amorphous material using the same process as in Production Examples 74 or 82, a procedure in accordance with these or a combination of these and conventional procedures, using 3-hydroxy-5-iodobenzoic acid methyl ester, (2R)-1-(tert-butyldimethylsiloxy)-2-hydroxypropane, 4-methanesulphonyl benzene thiol and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 1.30 (3H, d, J = 6.2 Hz), 3.05 (3H, s), 3.74-3.79 (2H, m), 3.81 (3H, s), 4.52-4.63 (1H, m), 6.78 (1H, d, J = 2.3 Hz), 7.21 (1H, m), 7.30 (1H, d, J = 2.2 Hz), 7.34 (2H, d, J = 8.6 Hz), 7.47-7.50 (1H, m), 7.51-7.54 (1H, m), 7.82 (2H, d, J = 8.6 Hz), 8.53 (1H, br).

ESI-MS (m/e) = 392 $(M+H)^+$

Production Example 134



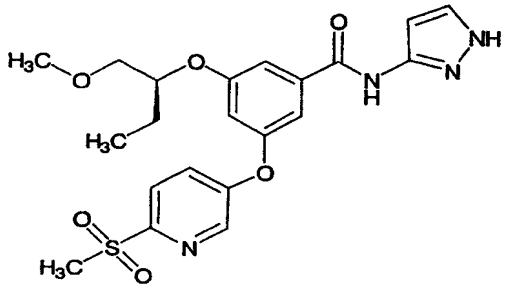
Preparation of 5-cyclopropyl oxy-3-(4-methanesulphonyl phenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 134 was obtained as a colourless oily substance using the same process as in Production Example 1, a procedure in accordance with this or a combination of such procedures, using p-methylthio phenyl boric acid, 3-amino-1-methyl-1H-pyrazole and 3-cyclopropyl oxy-5-methoxymethoxy-benzoic acid methyl ester obtained by reacting diethylzinc and diiodo-methane with 5-methoxymethoxy-3-vinyloxy-benzoic acid methyl ester obtained by reacting 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester with tetra vinyl tin and copper acetate.

^{1}H-NMR ($CDCl_3$) δ : 0.70-0.85 (m, 4H), 3.08 (s, 3H), 3.78 (m, 1H), 3.79 (s, 3H), 6.78 (m, 1H), 6.91 (m, 1H), 7.10-7.14 (m, 3H), 7.27 (m, 1H), 7.41 (m, 1H), 7.90 (d, 2H, J = 8.8 Hz), 8.52 (m, 1H).

ESI-MS (m/e) = 428 $(M+H)^+$

Production Example 135



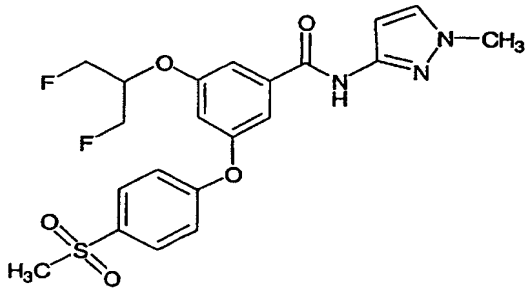
Preparation of 3-(6-methanesulphonyl pyridin-3-yloxy)-5-(1-methoxymethyl-propoxy)-N-(pyrazol-3-yl) benzamide

The compound of Production Example 135 was obtained as a colourless amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of such procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-methanesulphonyl pyridine .(2R)-1-methoxy-2-hydroxy butane and 3-amino-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 0.98 (t, 3H, J = 7.4 Hz), 1.69-1.78 (m, 2H), 3.22 (s, 3H), 3.38 (s, 3H), 3.58-3.59 (m, 2H), 4.37-4.43 (m, 1H), 6.84-6.85 (m, 2H), 7.20 (s, 1H), 7.41-7.49 (m, 3H), 8.04 (d, 1H, J = 8.6 Hz), 8.45 (d, 1H, J = 2.6 Hz), 9.92 (brs, 1H).

ESI-MS (m/e) = 461 $(M+H)^+$

Production Example 136



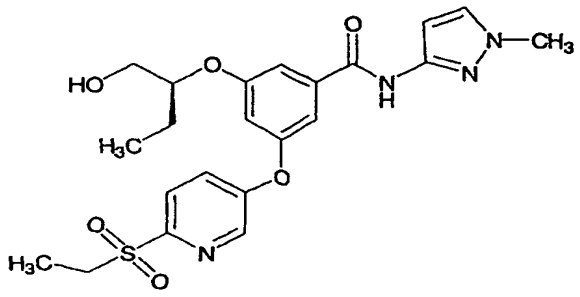
Preparation of 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(4-methanesulphonyl phenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 136 was obtained as a colourless amorphous material using the same process as in Production Example 89, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(4-methanesulphonyl-phenoxy)-5-methoxymethoxy-benzoic acid methyl ester obtained by Production Example 89, 1,3-difluoro-2-propanol and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 3.09 (s, 3H), 3.77 (s, 3H), 4.59-4.76 (m, 5H), 6.78 (s, 1H), 6.89 (t, 1H, J = 2.0 Hz), 7.13 (d, 2H, J = 8.6 Hz), 7.18 (s, 1H), 7.29 (d, 1H, J = 2.0 Hz), 7.33 (d, 1H, J = 2.0 Hz), 7.93

(d, 2H, J = 8.6 Hz), 8.76 (brs, 1H).
ESI-MS (m/e) = 466 $(M+H)^+$

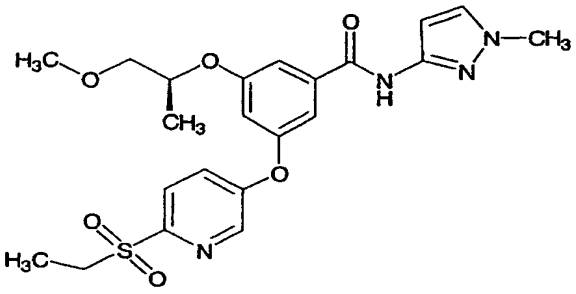
Production Example 137



Preparation of 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(1-hydroxymethyl-propoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 137 was obtained as a colourless amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-ethane sulfonyl pyridine, (2R)-1-(tert-butyldimethylsiloxy)-2-hydroxy butane and 3-amino-1-methyl-1H-pyrazole.
^{1}H-NMR ($CDCl_3$) δ : 0.97 (t, 3H, J = 7.4 Hz), 1.32 (t, 3H, J = 7.4Hz), 1.67-1.84 (m, 2H), 3.40 (q, 2H, J = 7.4 Hz), 3.74-3.84 (m, 5H), 4.33-4.40 (m, 1H), 6.77 (s, 1H), 6.79 (s, 1H), 7.15 (s, 1H), 7.28 (s, 1H), 7.33 (s, 1H), 7.43 (dd, 1H, J = 2.6, 8.8 Hz), 8.05 (d, 1H, J = 8.8 Hz), 8.47 (d, 1H, J = 2.6 Hz).
ESI-MS (m/e) = 475 $(M+H)^+$

Production Example 138



Preparation of 5-(6-ethane sulfonyl pyridin-3-yloxy)-3-(2-methoxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

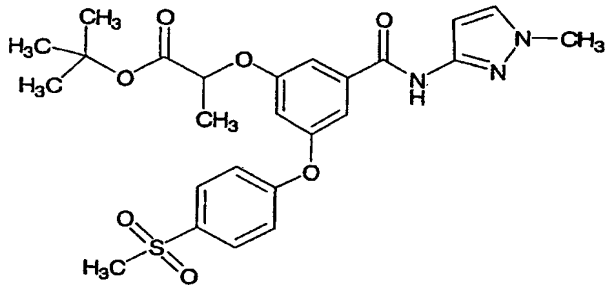
The compound of Production Example 138 was obtained as a colourless amorphous material using

the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-ethane sulfonyl pyridine, (2R)-2-hydroxy-1-methoxy propane and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 1.34 (t, 3H, J = 7.3 Hz), 1.34 (d, 3H, J = 4.0 Hz), 3.40 (s, 3H), 3.41 (q, 2H, J = 7.3 Hz), 3.49-3.60 (m, 2H), 3.80 (s, 3H), 4.60 (qt, 1H, J = 4.0, 6.2 Hz), 6.78 (s, 1H), 6.83 (d, 1H, J = 2.2 Hz), 7.14 (s, -IH), 7.28 (d, 1H, J = 2.2 Hz), 7r31(s, 1H), 7.42 (dd, 1H, J = 8.4, 2.6 Hz), 8.05 (d, 1H, J = 8.4 Hz), 8.48 (d, 1H, J = 2.6 Hz), 8.49 (brs, 1H).

ESI-MS (m/e) = 475 $(M=H)^+$, 473 $(M-H)^-$

Production Example 139



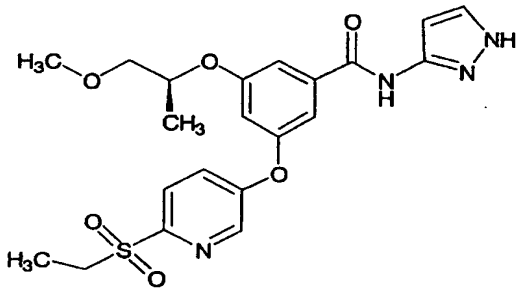
Preparation of 2-[3-(4-methanesulphonyl phenoxy)-5-(1-methyl-1H-pyrazol-3-yl carbamoyl)-phenoxy] propionic acid-tert-butyl ester

The compound of Production Example 139 was obtained as a colourless amorphous material using the same process as in Production Example 1, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-(4-methylthiophenoxy) benzoic acid methyl ester obtained by Production Example 1, 2-bromopropionic acid tert-butyl ester and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 1.44 (9H, s), 1.60 (3H, d, J = 6.8 Hz), 3.07 (3H, s), 3.81 (3H, s), 4.69 (1H, q, 1= 6/8Hg), 6.77 (1H, br), 7/10-7.16 (3H, m), 7.24 (1H, br), 7.29 (1H, d, J = 2.2 Hz), 7.92 (2H, d, J = 8.9 Hz), 8.38 (1H, br).

ESI MS(m/e) = 516 $(M+H)^+$

Production Example 140



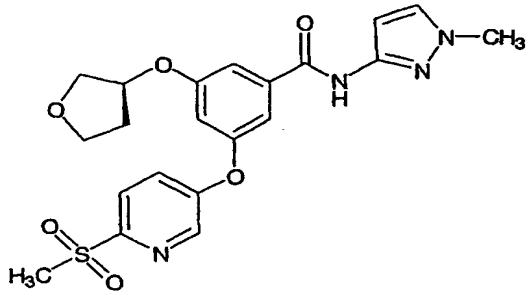
Preparation of 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(2-methoxy-1-methyl-ethoxy)-N-(pyrazol-3-yl)-benzamide

The compound of Production Example 140 was obtained as a colourless amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-ethane sulfonyl pyridine, (2R)-2-hydroxy-1-methoxy propane and 3-amino-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 1.33 (t, 3H, J = 7.3 Hz), 1.34 (d, 3H, J = 6.2 Hz), 3.40 (q, 2H, J = 7.3 Hz), 3.41 (s, 3H), 3.52-3.62 (m, 2H), 4.60-4.65 (m, 1H, J = 6.2Hz, -Hz), 6.83 (d, 1H, J = 2.2 Hz), 6.86 (s, 1H), 7.20 (s, 1H), 7.42 (d, 1H, J = 2.2 Hz), 7.42 (dd, 1H, J = 8.8, 2.6 Hz), 7.49 (s, 1H), 7.04 (d, 1H, J = 8.8 Hz), 8.47 (d, 1H, J = 2.6 Hz), 9.47 (brs, 1H).

ESI-MS (m/e) = 461 $(M+H)^+$, 459 $[M-H]^-$

Production Example 141



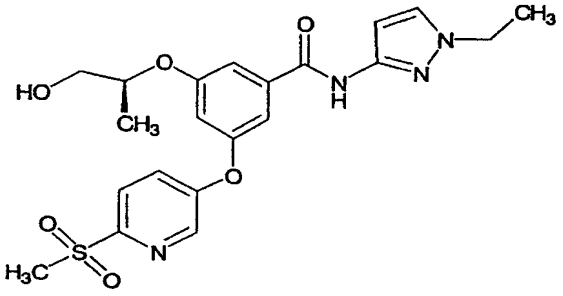
Preparation of 3-(6-methanesulphonyl pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl)-5-(tetrahydrofuran-3-yl) benzamide

The compound of Production Example 141 was obtained as a colourless amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-methanesulphonyl pyridine, (S)-(+)-3-hydroxytetrahydrofuran and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 2.15-2.26 (m, 1H), 2.26-2.30 (m, 1H), 3.24 (s, 3H), 3.80 (s, 3H), 3.88-4.03

(m, 4H), 4.97 (m, 1H), 6.76 (m, 2H), 7.11 (t, 1H, J = 2.2 Hz), 7.24 (d, 1H, J = 2.2 Hz) 7.28 (d, 1H, J = 2.2 Hz), 7,44 (dd, 1H, J = 2.9-8.4 Hz), 8.05 (d, 1H, J = 8.4 Hz), 8.44 (m, 1H), 8.45 (d, 1H, J = 2.9 Hz) ESI-MS (m/e) = 459 $(M+H)^+$

Production Example 142



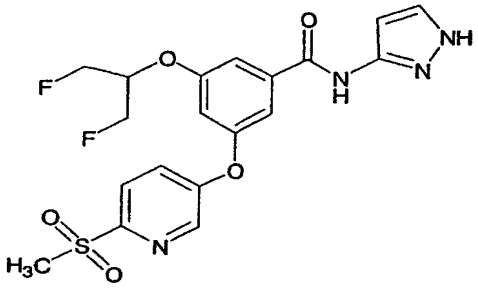
Preparation of N-(1-ethyl-1H-pyrazol-3-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methanesulphonyl pyridin-3-yloxy) benzamide

The compound of Production Example 142 was obtained as a white amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-methanesulphonyl pyridine, (2R)-1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 3-amino-1-ethyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 1.33 (d, 3H, J = 6.2 Hz), 1.47 (t, 3H,,J= 7.3 Hz), 1.98 (m, 1H), 3.24 (s, 3H), 3.77 (m, 2H), 4.07 (q, 2H, J = 7.3 Hz), 4.58 (m, 1H), 6.77 (d, 1H, J = 2.6 Hz), 6.82 (t, 1H, J = 2.6 Hz), 7.13 (m, 1H), 7.32 (m, 2H), 7.45 (dd, 1H, J = 2.6, 8.4 Hz), 8.06 (d, 1H, J = 8.4 Hz), 8.34 (m, 1H), 8.47 (d, 1H, J = 2.6 Hz).

ESI-MS (m/e) = 461 $(M+H)^+$

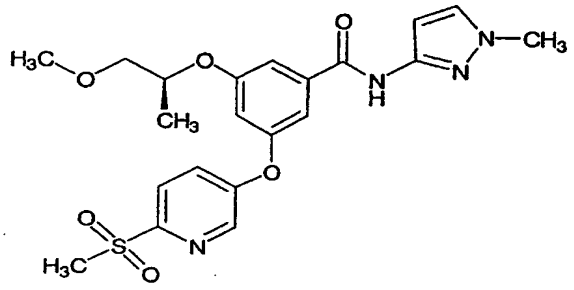
Production Example 143



Preparation of 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonyl pyridin-3-yloxy)-N-(pyrazol-3-yl) benzamide

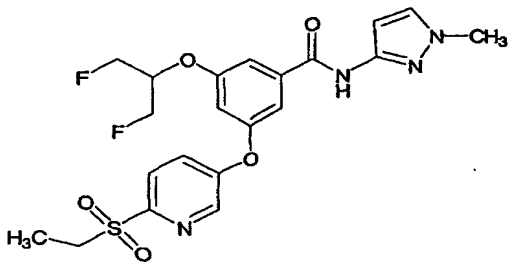
The compound of Production Example 143 was obtained as a white amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-methanesulphonyl pyridine, 1,3-difluoro-2-propanol and 3-amino-pyrazole.
^{1}H-NMR ($CDCl_3$) δ : 3.23 (s, 3H), 4.55-4.70 (m, 2H), 4.70-4.90 (m, 3H), 6.79 (m, 1H), 6.91 (m, 1H), 7.28 (m, 1H), 7.42-7.51 (m, 3H), 8.04 (d, 1H, J = 8.9 Hz), 8.44 (d, 1H, J = 2.6 Hz), 9.60 (m, 1H).
ESI-MS (m/e) = 453 $(M+H)^+$

Production Example 144



Preparation of 3-(6-methanesulphonyl pyridin-3-yloxy)-5-(2-methoxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide
The compound of Production Example 144 was obtained as a colourless oily substance using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-methanesulphonyl pyridine, (2R)-2-hydroxy-1-methoxy propane and 3-amino-1-methyl-1H-pyrazole.
^{1}H-NMR ($CDCl_3$) δ : 1.32 (d, 3H, J = 6.4 Hz), 3.23 (s, 3H), 3.40 (s, 3H), 3.54 (m, 2H), 3.78 (s, 3H), 4.59 (m, 1H), 6.78 (m, 1H), 6.84(m, 1H), 7.14 (m, 1H), 7.29 (m, 1H), 7.32 (m, 1H), 7.44 (dd, 1H, J = 2.6, 8.6 Hz), 8.05 (d, 1H, J = 8.6 Hz), 8.47 (d, 1H, J = 2.6 Hz), 8.66 (m, 1H).
ESI-MS (m/e) = 461 $(M+H)^+$

Production Example 145

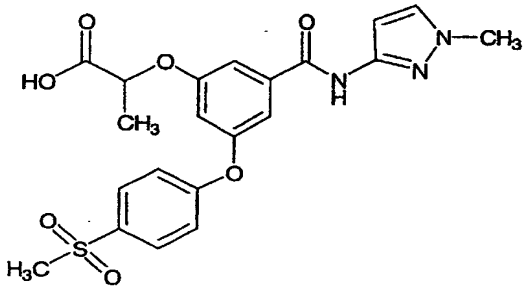


Preparation of 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(2-fluoro-1-fluoromethyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 145 was obtained as a colourless amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-ethane sulfonyl pyridine, 1,3-difluoro-2-propanol and 3-amino-1-methyl-1H-pyrazole.

1HNMR ($CDCl_3$) δ : 1.33 (t, 3H, J = 7.42 Hz), 3.41 (q, 2H, J = 7.4 Hz), 3.80 (s, 3H), 4.61-4.65 (m, 2H), 4.73-4.78 (m, 3H), 6.78 (dd, 1H, J = 2.0, 1.8 Hz), 6.91 (d, 1H, J = 2.3 Hz), 7.23 (dd, 1H, J = 1.8, 1.6 Hz), 7.30 (d, 1H, J = 2.3 Hz), 7.38 (dd, 1H, J = 2.0, 1.6 Hz), 7.16 (dd, 1H, J = 8.6, 2.7 Hz), 8.08 (d, 1H, J = 8.6 Hz), 8.50 (d, 1H, J = 2.7 Hz), 8.63 (brs, 1H).
ESI-MS (m/e) = 481 $(M+H)^+$, 479 $(M-H)^-$

Production Example 146

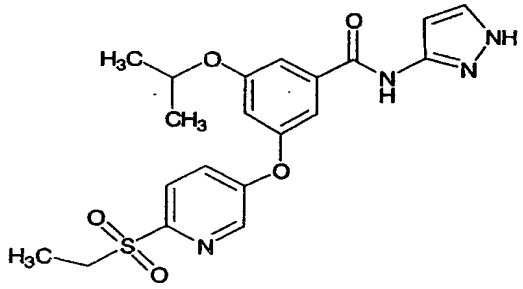


Preparation of 2-[3-(4-methanesulphonyl phenoxy)-5-(1-methyl-1H-pyrazol-3-yl carbamoyl)-phenoxy] propionic acid

The compound of Production Example 146 was obtained as a white solid by convernting the tert-butyl ester of the 2-[3-(4-methanesulphonyl phenoxy)-5-(1-methyl-1H-pyrazol-3-yl carbamoyl)-phenoxy] propionic acid-tert-butyl ester obtained by Production Example 139 to a carboxyl group. The process to transform ester into carboxyl group was carried out in accordance with Comprehensive Organic Transformations Richard L et al, VCHPublishers Co, 1988 and the like, a

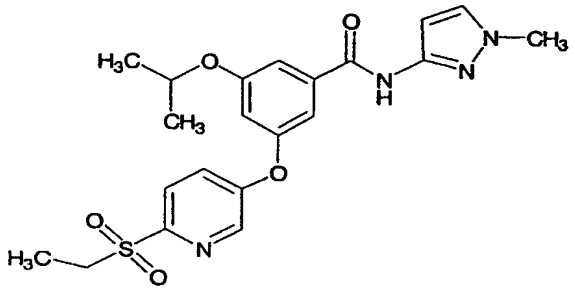
process in accordance with it or a combination of these with conventional procedures.
^{1}H-NMR (CD_3OD) δ = 1.60 (3H, d, J = 6.8 Hz), 3.11 (3H, s), 3.82 (3H, s), 6.54-6.58 (1H, br), 6.84 (1H, br), 7.16-7.28 (3H, m), 7.34 (1H, br), 7.49 (1H, d, J = 2.1 Hz), 7.95 (2H, d, J = 8.9 Hz).
ESI-MS (m/e) = 460 $(M+H)^+$

Production Example 147



Preparation of 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-isopropoxy-N-(pyrazol-3-yl) benzamide
The compound of Production Example 147 was obtained as a colourless amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-ethane sulfonyl pyridine, 2-hydroxypropane and 3-amino-pyrazole.
^{1}H-NMR ($CDCl_3$) δ : 1.32 (t, 3H, J = 7.3 Hz), 1.37 (d, 6H, J = 5.9 Hz), 3.39 (q, 2H, J = 7.3 Hz), 4.60 (septet, 1H, J = 5.9 Hz), 6.76 (dd, 1H, J = 2.2,2-2 Hz), 6.84 (s, 1H), 7.16 (s, 1H), 7.33 (s, 1H), 7.40 (dd, 1H, J = 8.8, 2.6 Hz), 7.51 (dd, 1H, J = 2.2,2-6 Hz), 8.03 (dd, 1H, J = 8.8, 2.6 Hz), 8.46 (dd, 1H, J = 2.6, 2.6 Hz), 9.03 (brs, 1H).
ESI-MS (m/e) = 431 $(M+H)^+$, 429 $(M-H)^-$

Production Example 148



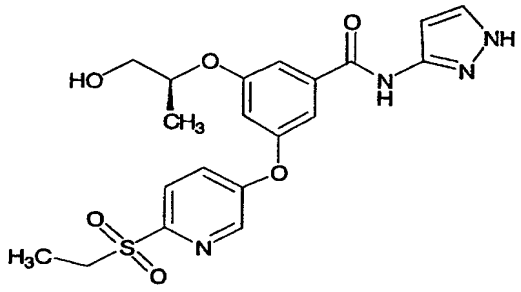
Preparation of 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-isopropoxy-N-(1-methyl-1H-pyrazol-3-yl) benzamide
The compound of Production Example 148 was obtained as a colourless amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a

combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-ethane sulfonyl pyridine, 2-hydroxypropane and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 1.34 (t, 3H, J = 7.3 Hz), 1.37 (d, 6H, J = 5.9 Hz), 3.41 (q, 2H, J = 7.3 Hz), 3.81 (s, 3H), 4.60 (septet, 1H, J = 5.9 Hz), 6.75-6.78 (m, 2H), 7.11 (s, 1H), 7.26 (s, 1H), 7.28 (d, 1H, J = 2.2 Hz), 7.42 (dd, 1H, J = 8.8, 2.9 Hz), 8.05 (d, 1H, J = 8.8 Hz), 8.36 (brs, 1H), 8.48 (d, 1H, J = 2.9 Hz).

ESI-MS (m/e) = 445 $(M+H)^+$, 443 $(M-H)^-$

Production Example 149



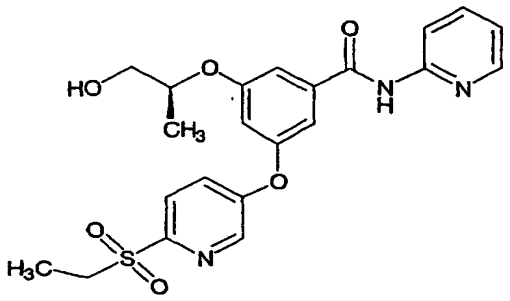
Preparation of 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(pyrazol-3-yl) benzamide

The compound of Production Example 149 was obtained as a colourless amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-ethane sulfonyl pyridine, (2R)-1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 3-amino-pyrazole.

^{1}H-NMR (CDC18.[one drop of CD30D]) δ = 1.29 (d, 3H, J = 6.3 Hz), 1.31 (t, 3H, J = 7.4 Hz), 3.39 (q, 2H, J = 7.4 Hz), 3.70-3.76 (m, 2H), 4.55 (septet, 1H, J = 6.3 Hz), 6.77 (s, 1H), 6.79 (d, 1H, J = 2.3 Hz), 7.20 (s, 1H), 7.37 (s, 1H), 7.41 (dd, 1H, J = 8.6, 2.7 Hz), 7.49 (d, 1H, J = 2.3 Hz), 8.02 (d, 1H, J = 8.6 Hz), 8.44 (d, 1H, J = 2.7 Hz), 9.55 (brs, 1H).

ESI-MS (m/e) = 447 $(M+H)^+$, 445 $(M-H)^-$

Production Example 150



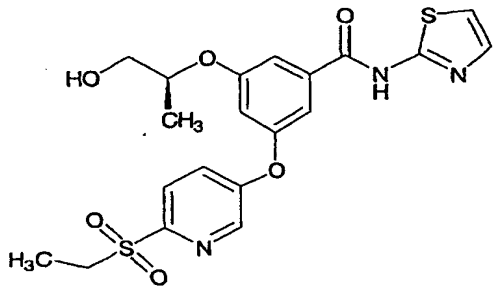
Preparation of 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(pyridin-2-yl) benzamide

The compound of Production Example 150 was obtained as a colourless amorphous substance using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-ethane sulfonyl pyridine, (2R)-1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 2-aminopyridine.

^{1}H-NMR ($CDCl_3$) δ : 1.33 (d, 3H, J = 6.1 Hz), 1.33 (t, 3H, J = 7.4 Hz), 3.41 (q, 2H, J = 7.4 Hz), 3.78-3.80 (m, 2H), 4.62 (dq, 1H, J = 4.5, 6.1 Hz), 6.84 (s, 1H), 7.11 (dd, 1H, J= 6.6, 5.1 Hz), 7.22 (s, 1H), 7.38 (s, 1H), 7.45 (dd, 1H, J = 8.8, 2.5 Hz), 7.78 (dd, 1H, J = 8.4, 6.6 Hz), 8.08 (d, 1H, J = 8.8 Hz), 8,30 (d, 1H, J = 5.1 Hz), 8.34 (d, 1H, J = 8.4 Hz), 8.50 (d, 1H, J = 2.5 Hz), 8-63 (brs, 1H).

ESI-MS(m/e)= 481[M+H]+.

Production Example 151



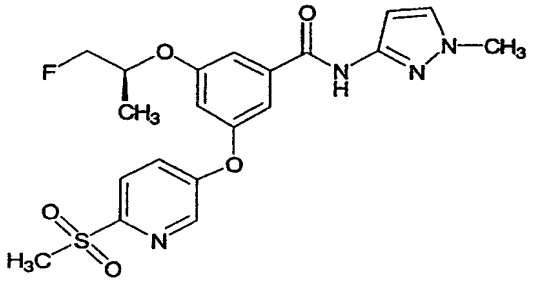
Preparation of 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide

The compound of Production Example 151 was obtained as a colourless amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-ethane sulfonyl pyridine, (2R)-1-(tert-butyldimethylsiloxy)-2-hydroxypropane and 2-aminothiazole.

^{1}H-NMR ($CDCl_3$) δ : 1.31 (d, 3H, J = 6.3 Hz), 1.33 (t, 3H, J = 7.4 Hz), 3.41 (q, 2H, J = 714 Hz), 3.76-3.78 (m, 2H), 4.55-4.60 (m, 1H), 6.86 (m, 1H), 7.02 (d, 1H, J = 3.5 Hz), 7.26 (m, 1H), 7.29 (d, 1H, J = 3.5 Hz), 7.42 (m, 1H), 7.46 (dd, 1H, J = 8.6, 2.7 Hz), 8.08 (d, 1H, J = 8.6 Hz), 8.49 (d, 1H, J = 2.7 Hz).

ESI-MS (m/e) = 464 $(M+H)^+$, 462 $(M-H)^-$

Production Example 152



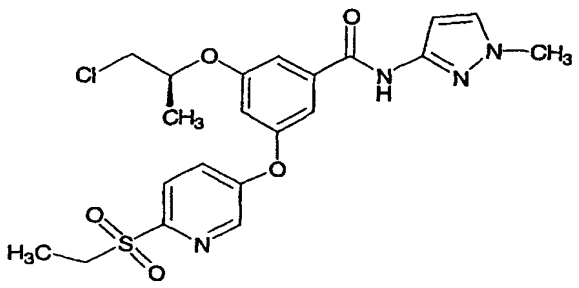
Preparation of 5-(2-fluoro-1-methyl-ethoxy)-3-(6-methanesulphonyl pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 152 was obtained as a colourless amorphous material by converting the hydroxy group of 5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methanesulphonyl pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide obtained in Production Example 126 into mesylate using methane sulphonyl chloride and triethylamine and thereafter reacting with tetrabutyl ammonium fluoride.

^{1}H-NMR ($CDCl_3$) δ : 1.35 (dd, 3H, J = 1.6, 6.2 Hz), 3.24 (s, 3H), 3.77 (s, 3H), 4.45 (m, 1H), 4.57 (m, 1H), 4.67 (m, 1H), 6.79 (d, 1H, J = 2.3 Hz), 6.84 (t, 1H, J = 2.3 Hz), 7.16 (t, 1H, J = 2.3 Hz), 7.30 (d, 1H, J2.3 Hz), 7.32 (m, 1H), 7.45 (d, 1H, J = 2.3, 8.6 Hz), 8.06 (d, 1H, J = 8.6 Hz), 8.47 (d, 1H, J = 2.3 Hz), 8.79 (m, 1H).

ESI-MS(M/E) = 449 $(M+H)^+$

Production Example 153



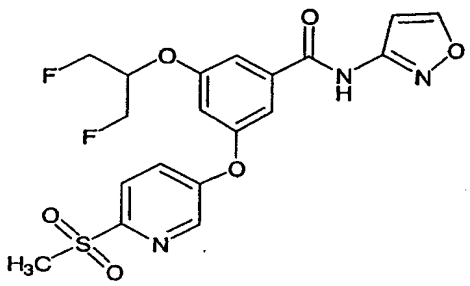
Preparation of 5-(2-chloro-1-methyl-ethoxy)-3-(6-ethane sulfonyl pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 153 was obtained as colourless amorphous substance by converting hydroxy group of 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide obtained by Production Example 117 into mesylate by using triethylamine and methane sulphonyl chloride.

^{1}H-NMR ($CDCl_3$) δ : 1.33 (t, 3H, J = 7.4 Hz), 1.45 (d, 3H, J = 6.2 Hz), 3.41 (q, 2H, J = 7.4 Hz), 3.63 (dd, 1H, J = 5.0, 11.5h2), 3.69 (dd, 1H, J = 5.0, 11.5 Hz), 3.79 (s, 3H), 4.62 (m, 1H), 6.79 (d, 1H, J = 2.2 Hz), 6.83 (t, 1H, i2.2 Hz), 7.18 (m, 1H), 7.29-7.35 (m, 2H), 7.45 (dd, 1H, J = 2.7, 8.6 Hz), 8.07 (d, 1H, J = 8.6 Hz), 8.49 (d, 1H, J = 2.7 Hz), 8.67 (m, 1H).

ESI... MS(M/B) = 479 $(M+H)^+$

Production Example 154



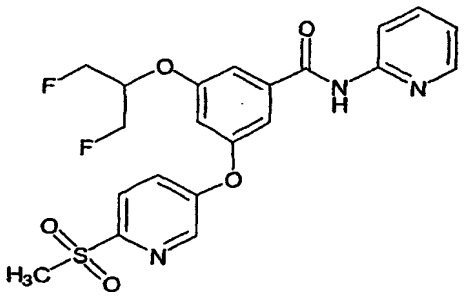
Preparation of(5-(2-fluoro-1-fluoromethyl-ethoxy)-N-(isoxazol-3-yl)-3-(6-methanesulphonyl pyridin-3-yloxy) benzamide.

The compound of Production Example 154 was obtained as a white amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-methanesulphonyl pyridine, 1,3-difluoro-2-propanol and 3-aminooxazole.

^{1}H-NMR ($CDCl_3$). δ = 3.24 (s, 3H), 4.59-4.70 (m, 2H), 4.70-4.90 (m, 3H), 6.96 (t, 1H, J = 2.3 Hz), 7.19(m, 1H), 7.32 (m, 1H), 7.45(m, 1H), 7.48 (dd, 1H, J = 2.7, 8.5 Hz), 8.09 (d, 1H, J = 8.5 Hz), 8.29 (m, 1H), 8.49 (d, 1H, J = 2.7 Hz), 9.60 (m, 1H).

ESI-MS(M/E) = 454 $(M+H)^+$

Production Example 155



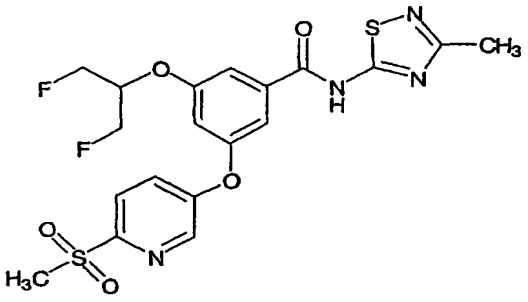
Preparation of 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonyl pyridin-3-yloxy)-N-(pyridin-2-yl) benzamide

The compound of Production Example 155 was obtained as a white amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-methanesulphonyl pyridine, 1,3-difluoro-2-propanol and 2-aminopyridine.

^{1}H-NMR ($CDCl_3$) δ : 3.24 (s, 3H), 4.60-4.70 (m, 2H), 4.70-4.90 (m, 3H), 6.93 (t, 1H, J = 2.1H poly), 7.10 (m, 1H), 7.26 (m, 1H), 7.42(mIH),,7.48 (dd, 1H, J = 2,1,8,2 Hz), 7.78 (dt, 1H, J= (sic)), 8.09 (d, 1H, J = 8.4 Hz), 8.30 (m, 1H), 8.32 (d, 1H, J = 8.4 Hz), 8.49 (d, 1H, J = 2.1 Hz), 8.59 (br, 1H).

ESI-MS(M/E) = 464 $(M+H)^+$

Production Example 156



Preparation of 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonyl pyridin-3-yloxy)-N-(3-methyl-[1,2,4]-thiadiazol-5-yl) benzamide

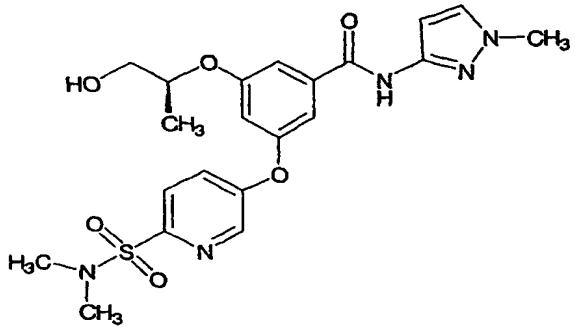
The compound of Production Example 156 was obtained as a white amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-methanesulphonyl pyridine, 1,3-difluoro-2-propanol and 5-amino-3-methyl-[1,2,4] thiadiazole.

^{1}H-NMR ($CDCl_3$) δ : 2.50 (s, 3H), 3.27 (s, 3H), 4.57-4.67 (m, 2H), 4.67-4.90 (m, 3H), 7.01 (t, 1H,

J = 2.3Hl), 7.29 (m, 1H), 7.45 (m, 1H), 7.49 (dd, 1H, J = 2.3, 8.7 Hz), 8.09 (d, 1H, J = 8.7 Hz), 8.47 (d, 1H, J = 2.3 Hz).

ESI-MS(M/E) = 485 $(M+H)^+$

Production Example 157



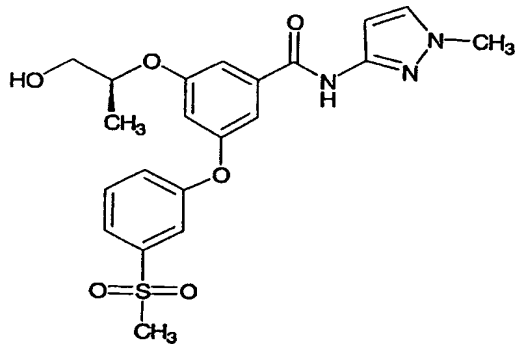
Preparation of 3-(4-dimethyl sulphamoyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 157 was obtained as a white amorphous material using the same process as in Production Example 42, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 4 –bromo-dimmethylsulphamoyl benzene, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 3-amino-1-methyl-1H-pyrazole.

1HNMR ($CDCl_3$) δ : 1.31 (d, 3H, J = 6.3Hz), 2.19 (brs, 1H), 2.74 (s, 6H), 3.76-3.80 (m, 2H), 3.81 (s, 3H), 4.54-4.59 (m, 1H, J = 6.3Hz, -Hz (sic)), 6.79 (m, 1H), 6.81 (m, 1H), 7.11 (d, 2H, J = 9.0 Hz), 7.13 (s, 1H), 7.29-7.30 (m, 2H), 7.77 (d, 2H, J = 9.0 Hz), 8.55 (m, 1H).

ESI-MS (m/e) = 475 $(M+H)^+$, 473 $(M-H)^-$

Production Example 158



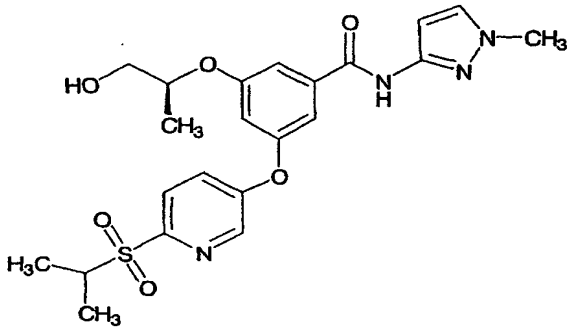
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(3-methanesulphonyl phenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 158 was obtained as a white amorphous material using the same process as in Production Example 1 or 89, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 3-methylthio-phenyl boric acid, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 1.30 (d, 3H, J = 6.2Hz), 2.08 (t, 1H, J-= 6.5 Hz), 3.07 (s, 3H), 3.73-3.78 (m, 5H), 4.52-4.57 (m, 1H), 6.77-6.78 (m, 2H), 7.08 (d, 1H, J = 2.1 Hz), 7.25-7.31 (m, 3H), 7.54 (t, 1H, J = 7.6 Hz), 7.59 (d, 1H, J = 2.1 Hz), 7.70 (d, 1H, J = 7.6 Hz), 8.49 (brs, 1H).

ESI-MS (m/e) = 446 $(M+H)^+$

Production Example 159



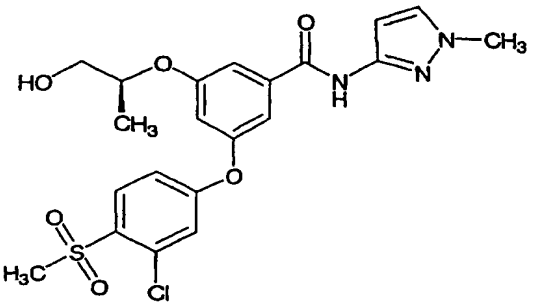
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-3-(6-isopropyl sulfonyl pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 159 was obtained as a white amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 5-bromo-2-isopropyl sulfonyl pyridine, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 1.31 (d, 3H, J = 5.9 Hz), 1.35 (d, 6H, J = 6.7 Hz), 2.25 (brs, 1H), 3.72 (septet, 1H, J = 6.7 Hz), 3.70-3.81 (gourd, 2H), 3.81 (s, 3H), 4/53-4-59 (m, 1H), 6.78-6.79(m, 1H), 6.80-6.82 (m, 1H), 7.17 (m, 1H), 7.29-7.31 (m, 1H), 7.32 (m, 1H), 7.43 (2.7 Hz), 8.06 (d, 1H, J = 8.6 Hz), 8.50 (d, 1H, J = 2.7 Hz), 8.60 (brs, 1H).

ESI-MS (m/e) = 475 $(M+H)^+$, 473 $(M-H)^-$

Production Example 160



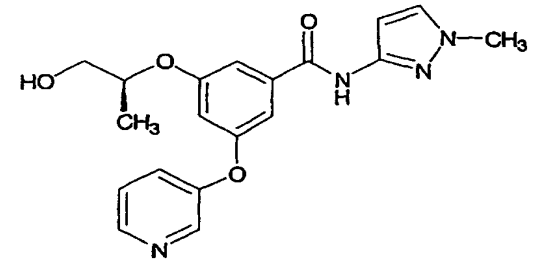
Preparation of 3-(3-chloro-4-methanesulphonyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl - 1H-pyrazol-3-yl) benzamide

The compound of Production Example 160 was obtained as a white amorphous using the same process as in Production Example 42, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 4-bromo-2-chloro-methanesulphonyl benzene, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 1.31 (d, 3H, J = 6.1 Hz), 3.28 (s, 3H), 3.76-3.80 (m, 5H), 4.54-4.59 (m, 1H), 6.80-6.81 (m, 2H), 7.02 (dd, 1H, J = 2.3, 8.8 Hz), 7.14-7.15 (m, 2H), 7.30 (d, 1H, J = 2.3 Hz), 7.33 (s, 1H), 8.11 (d, 1H, J = 8.8 Hz), 8.75 (brs, 1H).

ESI-MS (m/e) = 480 $(M+H)^+$

Production Example 161



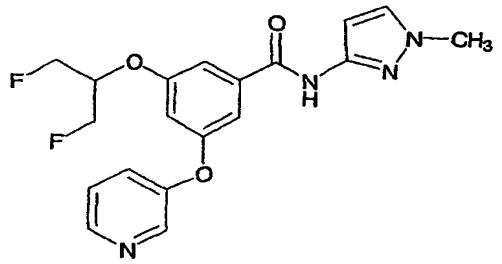
Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(pyridin-3-yloxy) benzamide

The compound of Production Example 161 was obtained as a white amorphous substance using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 3-iodopyridine, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 1.30 (d, 3H, J = 6.3 Hz), 2.27 (m, 1H), 3.72-3.80 (m, 2H), 3.80 (s, 3H), 4.55

(m, 1H), 6.75 (t, 1H, J = 2.3 Hz), 6.79 (d, IH9 J= 2.3 Hz), 7.05 (m, 1H), 7.22 (m, 1H), 7.29 (d, 1H, J = 2.8 Hz), 7.31-7.38 (m, 2H), 8.44 (m, 2H), 8.62 (m, 1H).
ESI-MS(M/E) = 369 $(M+H)^+$

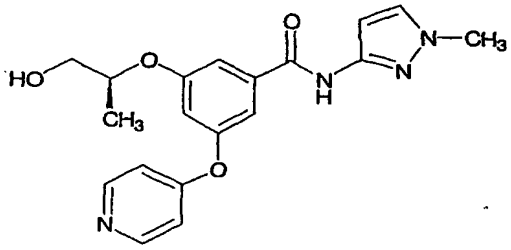
Production Example 162



Preparation of 5-(2-fluoro-1-fluoromethyl - ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(pyridin-3-yloxy) benzamide

The compound of Production Example 162 was obtained as a white amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 3-iodopyridine, 1,3-difluoro-2-propanol and 3-amino-1-methyl-1H-pyrazole.
^{1}H-NMR ($CDCl_3$) δ : 3.77 (s, 3H), 4.55-4.67 (m, 2H), 4.67 (m, 3H), 6.79 (d, 1H, J = 2.3 Hz), 6.82 (t, 1H, J = 2.3 Hz), 7.11 (m, 1H), 7.26 (m, 1H), 7.29 (d, 1H, J = 2.3 Hz), 7.30-7.38 (m, 2H), 8.45 (m, 2H), 8.70 (m, 1H).
ESI-MS (m/e) = 389 $(M+H)^+$

Production Example 163



Preparation of 5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(pyridin-4-yloxy) benzamide.

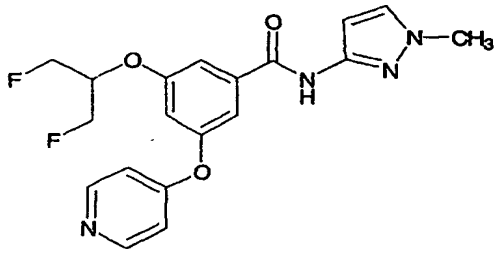
The compound of Production Example 163 was obtained as a white amorphous using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxymethoxy benzoic acid methyl ester, 4-chloropyridine hydrochloride, (2R)-1-(t-butyldimethylsiloxy)-2-hydroxypropane and 3-amino-1-

methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 1.31 (d, 3H, J = 6.3 Hz), 2.05 (m, 1H), 3.77 (m, 2H), 3.82 (s, 3H), 4.56 (m, 1H), 6.79 (d, 1H, J = 2.3 Hz), 6.83 (t, 1H, J = 2.3 Hz), 6.88 (dd, 2H, J = 1.6, 4.7 Hz), 7.15 (m, 1H), 7.30 (d, 1H, J = 2.2 Hz), 7.83 (m, 1H), 8.42 (m, 1H), 8.51 (dd, 2H, J = 1.6, 4,7 Hz)

ES1-MS(M/E)= 369 $(M+H)^+$

Production Example 164



Preparation of 2-[3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(1-methyl-1H-pyrazol-3-yl carbamoyl)-phenoxy] propionic acid

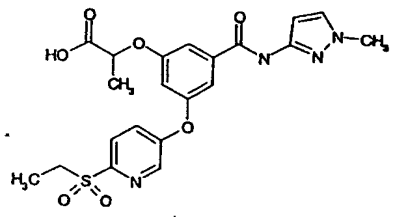
The compound of Production Example 164 was obtained as a white amorphous material using the same process as in Production Example 117, a procedure in accordance with this or a combination of these and conventional procedures, using 5-hydroxy-3-methoxy methoxy benzoic acid methyl ester,

4-chloropyridine hydrochloride, 1,3-difluoro-2-propanol and 3-amino-1-methyl-1H-pyrazole.

^{1}H-NMR ($CDCl_3$) δ : 3.81 (s, 3H), 4.58-4.67 (m, 2H), 4.67-4.82 (m, 3H), 6.79 (d, 1H, J = 2.0 Hz), 6.89 (dd, 2H, J = 1.6, 4.7 Hz), 6.91 (t, 1H, J2.3 Hz), 7.21 (t, 1H, J = 2.3 Hz), 7.30 (d, 1H, J = 2.0 Hz), 7.38 (t, 1H, J = 2.3 Hz), 8.52 (m, 1H), 8.52 (dd, 2H, J = 1.6, 4.7 Hz).

ESI-MS(M/E) = 389 $(M+H)^+$

Production Example 165



Preparation of 2-[3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(1-methyl-1H-pyrazol-3-yl carbamoyl)-phenoxy] propionic acid

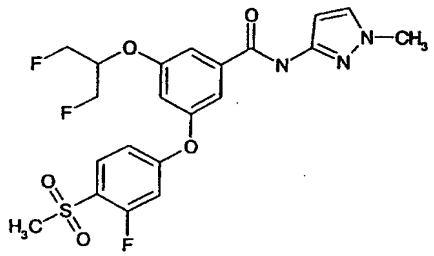
The compound of Production Example 165 was obtained as a white solid by converting the tert-butyl ester of 2-[3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(1-methyl-1H-pyrazol-3-yl carbamoyl)-

phenoxy] propionic acid-tert-butyl ester obtained using the same method as in Production Example 1, using 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-hydroxy-benzoic acid methyl ester obtained by Production Example 117, 2-bromopropionic acid tert-butyl ester and 3-amino-1-methyl-1H-pyrazole, to a carboxyl group. The process to transform ester into carboxyl group was carried out in accordance with a literature method (for examplel Comprehensive Organic Transformations, Richard L, VCH Publishers Co, 1988 and the like), method in accordance with this or a combination of these and conventional methods.

^{1}H-NMR ($CDCl_3$) δ : 1.24 (3H, t, J = 7.4 Hz), 1.59 (3H, d, J = 6.8 Hz), 3.39 (2H, q, J = 7.4 Hz), 3.81 (3H, s), 4.69-4.80 (1H, m), 6.56 (1H, d, J = 2.3 Hz), 6.90 (1H, t, J = 2.2 Hz), 7.25 (1H, br), 7.37 (1H, br), 7.48 (1H, d, J = 2.3 Hz), 7.62 (1H, dd, J = 8.7Hz, 2.7 Hz), 8.07 (1H, d, J = 6.4 Hz), 8.52 (1H, d, J = 2.7 Hz).

ESI-MS(M/E) = 475 $(M+H)^+$

Production Example 166



Preparation of 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(3-fluoro-4-methanesulphonyl phenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide

The compound of Production Example 166 was obtained as a colourless amorphous material using the same process as in Production Example 2, a procedure in accordance with this or a combination of these and conventional procedures, using 3-(3-fluoro-4-methanesulphonyl phenoxy)-5-hydroxy - benzoic acid methyl ester obtained using the same process as in Production Example 42, 1,3-difluoro-2-propanol and 3-amino-1-methyl-1H-pyrazole.

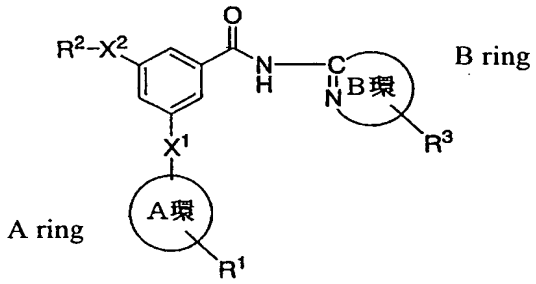
^{1}H-NMR ($CDCl_3$) δ : 3.23 (3H, s), 3.82 (3H, s). 4.61-4.78 (5H, m), 6.78 (1H, d, J = 2.3 Hz), 6.83-6.94 (3H, m), 7.19 (1H, t, J = 1.8 Hz), 7.30 (1H, d, J = 2.3 Hz), 7.38 (1H, t, J = 1.8 Hz), 7.94 (1H, t, J = 8.4 Hz), 8.37 (1H, brs)ES1-MS(M/E) = 484 $(M+H)^+$

Possible Applications in Industry

Heteroaryl carbamoyl benzenes represented by formula (1) in accordance with this invention is useful in the prevention and/or therapy of obesity or diabetes mellitus and diabetes mellitus complication in a sphere of drug by showing excellent glucokinase activity.

Patent Claims

1. A compound of formula (I)

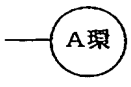


(I)

or pharmacologically acceptable salts thereof

[wherein, X1 denotes an oxygen atom, sulfur atom or NH, and X2 denotes oxygen atom, sulfur atom or CH_2, R1 denotes one or two substituents that may be present on the ring A selected from the group comprising alkylsulfonyl group, alkanoyl group, lower alkyl group, hydroxyalkyl group, hydroxy group, alkylcarbamoyl group, alkyl sulphamoyl group, dialkyl sulphamoyl group, alkylthio group, alkoxy group, dialkyl carbamoyl group, alkoxycarbonylamino group, alkoxycarbonyl group, halogen atom, alkanoyl amino alkyl group, alkoxycarbonylamino alkyl group, alkylsulfonyl amino alkyl group, cyano group and trifluoromethyl group. R2 denotes straight chain or branched lower alkenyl group or lower alkyl group, or 3-7C cyclic alkyl group (wherein 1 carbon atom among the carbon atoms composing said ring (except the carbon atom bonded to X2) may be replaced with oxygen atom, NH, N-alkanoyl group or CONH), that may have substituents selected from the group comprising halogen atom, carboxyl group, alkoxycarbonyl group, hydroxy group, amino group (also said amino group may be substituted by one or two alkanoyl group or lower alkyl group), alkoxy group and N-alkylcarbamoyl group. R3 denotes one or two substituents that may be present on B ring selected from the group comprising the lower alkyl group, alkoxy group, alkylamino group, lower dialkylamino group, halogen atom, trifluoromethyl group, hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be substituted by lower alkyl group), amino alkyl group, alkanoyl group, carboxyl group, alkoxycarbonyl group and cyano group.

The formula (II)



(II)

denotes an aryl group of 6-10 members or a heteroaryl group of 5-7 members, which may have 1 or 2

substituents represented by the aforesaid R1 in ring,
and the formula (III)

B ring

(III)

denotes a monocyclic or bicyclic heteroaryl ring where the carbon atom in the B ring which is bonded to the nitrogen atom of the amide group of formula (I) forms C=N with a nitrogen atom in said ring].

2. A compound in accordance with Claim 1 or pharmacologically acceptable salts thereof, wherein X1 is O or S and X2 is O or CH2.

3. A compound in accordance with Claim 2, wherein the A ring is phenyl group or 5-6 membered heteroaryl group, or pharmacologically acceptable salts thereof.

4. A compound in accordance with Claim 2, wherein the A ring is phenyl group.

5. A compound in accordance with Claim 2, wherein the A ring is 5 to 6 membered heteroaryl group.

6. A compound in accordance with any of Claim 4 or 5 or pharmacologically acceptable salts thereof, wherein R1 is alkylsulfonyl group, alkanoyl group, hydroxyalkyl group, alkylcarbamoyl group, alkyl sulphamoyl group, dialkyl sulphamoyl group, dialkyl carbamoyl group, alkoxycarbonylamino group, halogen atom, alkanoyl amino alkyl group, alkylsulfonyl amino alkyl group, alkoxycarbonylamino alkyl group.

7. A compound in accordance with Claim 4 or pharmacologically acceptable salts thereof, wherein the R1 is alkylsulfonyl group, alkanoyl group, hydroxyalkyl group, alkanoyl amino alkyl group, alkylsulfonyl amino alkyl group, alkoxycarbonylamino alkyl group.

8. A compound or pharmacologically acceptable salts thereof in accordance with Claim 4, wherein the R1 is alkylsulfonyl group, alkanoyl group, hydroxyalkyl group.

9. A compound in accordance with any of Claims 3-8 or pharmacologically acceptable salts thereof, wherein the monocyclic or bicyclic heteroaryl ring where the carbon atom in the B ring which is

bonded to the nitrogen atom of the amide group of formula (I) forms C=N with a nitrogen atom in said ring and which may have 1 or 2 substituents represented by the aforesaid R3 in said ring, (except the case that said heteroaryl group is 5-alkoxycarbonyl-pyridin-2-yl group or 5-carboxyl-pyridin-2-yl group).

10. A compound in accordance with Claim 7 or pharmacologically acceptable salts thereof, wherein the B ring has at least one heteroatom selected from the group comprising nitrogen atom, sulfur atom and oxygen atom, in addition to the nitrogen atom forming C=N with carbon atom in said ring bonded with nitrogen atom of amide group of the said formula (I).

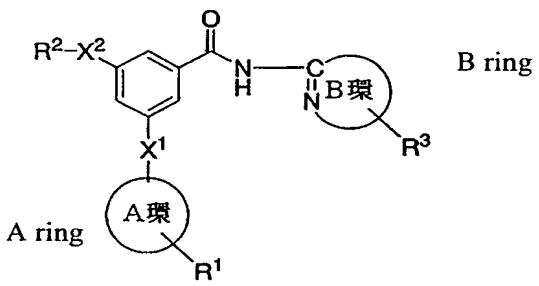
11. A compound in accordance with any of Claims 1-10 or pharmacologically acceptable salts thereof, wherein R2 is 3-7C cyclic alkyl group (1 of carbon atom composing said ring may be substituted by oxygen atom, NH or N-alkanoyl group), straight or branched chain lower alkyl group or lower alkenyl group, which may be substituted by halogen atom, carboxyl group, alkoxycarbonyl group, hydroxy group, amino group (also said amino group may be substituted by lower alkyl group of 1 or 2), alkoxy group, N-alkylcarbamoyl group or alkanoyl amino group.

12. A compound in accordance with any of Claims 1-11 or pharmacologically acceptable salts thereof, wherein the B ring is thiazolyl group, imidazolyl group, isothiazolyl group, thiadiazolyl group, triazolyl group, oxazolyl group, isoxazolyl group, pyrazinyl group, pyridazinyl group, pyrazolyl group, pyrimidinyl group, pyrido thiazolyl group or benzothiazolyl group.

13. A compound in accordance with any of Claims 1-12 or pharmacologically acceptable salts thereof, wherein R3 is lower alkyl group, alkoxy group, halogen atom, hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be substituted by lower alkyl group), amino alkyl group or alkanoyl group.

14. A compound in accordance with any of Claims 1 to 12 or pharmacologically acceptable salts thereof, wherein R3 is lower alkyl group, hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be substituted by lower alkyl group).

15. The compounds represented by formula (I)



(I)

(each symbol is the same as above) are the compounds which are 5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-(4-methylthiazol-2-yl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-ethoxy-3-(4-methanesulphonylphenoxy)-N-(4-methoxymethyl-thiazol-2-yl) benzamide, 5-cyclopentyl oxy-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yloxy)-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methoxymethyl-ethoxy)-N-thiazol-2-yl-benzamide, 3-(2-fluoro-4-methanesulphonylphenoxy)-5-isopropoxy-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, 5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-pyrazol-3-yl-benzamide, 5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-pyrazin-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(3-methoxy-1-methyl-propoxy)-N-thiazol-2-yl-benzamide, 5-(3-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-pyrimidin-4-yl-benzamide, 5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-(pyrimidin-2-yl)-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzamide, N-(isoxazol-3-yl)-3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-benzamide, 3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-N-[1,3,4] thiadiazol-2-yl-benzamide, 5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-5-(1-methoxymethyl-propoxy)-benzamide, 5-(2-amino-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(2-dimethylamino-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-propoxy)-3-(4-methanesulphonylphenoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, 3-(4-methanesulphonylphenoxy)-5-(2-methoxy-propoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, 5-isopropoxy-3-(4-methanesulphonylphenoxy)-N-(thiazolo [5,4-b] pyridin-2-yl)-benzamide, 5-(2-hydroxymethyl-allyl)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazolo [5,4-b] pyridin-2-yl-

benzamide, 5-(3-hydroxy-2-methyl-propyl)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-N-(4-methyl-thiazol-2-yl)-5-(piperidin-4-yl-oxy)-benzamide hydrochloride, 5-(1-acetyl-piperidin-4-yloxy)-3-(4-methanesulphonylphenoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, 2-[3-(4-methanesulphonylphenoxy)-5-(4-methyl-thiazol-2-yl-carbamoyl)-phenoxy] propionic acid, 5-(3-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 3-(4-methanesulphonylphenoxy)-5-(1-methylcarbamoyl-ethoxy)-N-(4-methyl-thiazol-2-yl)-benzamide, 5-(2-acetylamino-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-pyridin-2-yl-benzamide, 5-(2-hydroxy-ethoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-cyclopentyl oxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, N-(4-acetyl-thiazol-2-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy) benzamide, 3-(3-fluoro-4-methanesulphonylphenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(5-methyl-thiazol-2-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-([1,2,4] thiadiazol-5-yl)-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(5-methoxycarbonyl-pyridin-2-yl)-benzamide, 6-[5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzoylamino] nicotinic acid, 5-(2-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl)-3-(4-methanesulphonylphenoxy)-benzamide, N-(5-hydroxymethyl-thiazol-2-yl)-5-isopropoxy-3-(4-methanesulphonylphenoxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide, N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(2-methylthiazol-4-yl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(4-methoxymethyl-thiazol-2-yl)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide, N-[4-(1-hydroxy-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy)-5-(tetrahydrofuran-3-yl-oxy)-benzamide, N-(2,5-dimethyl thiazol-4-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-benzamide, 5-isopropoxy-3-(4-methoxycarbonylamino methylphenoxy)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(4-methylcarbamoyl-phenoxy)-N-thiazol-2-yl-benzamide,

3-(4-dimethylcarbamoyl-phenoxy)-5-isopropoxy-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(4-methyl carbonylamino methyl-phenoxy)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(4-methanesulphonyl aminomethyl-phenoxy)-N-thiazol-2-yl-benzamide, 3-[4-(1-hydroxy-propyl)-phenoxy]-5-isopropoxy-N-thiazol-2-yl-benzamide, 6-[3-isopropoxy-5-(thiazol-2-yl carbamoyl)-phenoxy]-nicotinic acid methyl ester, 3-(5-hydroxymethyl-pyridin-2-yl-oxy)-5-isopropoxy-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(5-methanesulphonyl pyridin-2-yl)-N-thiazol-2-yl-benzamide, 3-(5-acetyl-pyridin-2-yl-oxy)-5-isopropoxy-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(5-methoxycarbonyl-pyrazin-2-yl-oxy)-N-thiazol-2-yl-benzamide, 3-(5-cyano-pyridin-2-yl-oxy)-5-isopropoxy-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(2-oxo-1,2-dihydro-pyridin-4-yl-oxy)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(2-oxo-1,2-dihydro-pyridin-3-yl-oxy)-N-thiazole-2-yl-benzamide, 5-isopropoxy-3-(2-oxo-1,2-dihydro-pyridin-3-yl-oxy)-N-thiazolo [5,4-b] pyridin-2-yl-benzamide, 5-isopropoxy-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazolo [5,4-b]-pyridin-2-yl-benzamide, 5-isopropoxy-3-(4-methyl-[1,2,4] triazol-3-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-thiazol-2-yl sulphanyl-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(4H-[1,2,4] triazol-3-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(5-methyl sulphanyl-[1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-isopropoxy-3-(5-methyl-[1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-(tetrahydrofuran-3-yl-oxy)-N-thiazol-2-yl-3-(4H-[1,2,4] triazol-3-yl sulphanyl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(4-methyl-thiazol-2-yl)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-benzamide, 5-(3-hydroxy-1-methyl-propoxy)-N-(4-methyl-thiazol-2-yl)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenyl sulphanyl)-N-thiazol-2-yl-benzamide, 3-(3-fluoro-phenylthio)-5-(2-hydroxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(pyridin-4-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methyl-pyridin-3-yl sulphanyl)-N-thiazol-2-yl-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(3-methyl-[1,2,4]-thiadiazol-5-yl)-benzamide, N-[3-hydroxymethyl-1,2,4-thiadiazol-5-yl]-3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy) benzamide, 5-(3-hydroxy-1-methyl ethoxy)-3-(4-methanesulphonylphenoxy)-N-[5-methyl-1,2,4-thiadiazol-3-yl] benzamide, 5-(hydroxy-1-methyl ethoxy)-3-(4-methanesulphonylphenoxy)-N-(3-methoxy-1,2,4-thiadiazol-5-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(1,2,5-thiadiazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(4-trifluoromethyl-thiazol-2-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(4,5,6,7-tetrahydrobenzo thiazol-2-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(pyridazin-3-yl)-benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(3-isopropyl-[1,2,4]-triazol-5-yl)-3-(4-methanesulphonylphenoxy) benzamide, 5-(2-

hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(3-methyl-[1,2,4]-oxadiazol-5-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-[4-(1-hydroxy-1-methyl-ethyl)-thiazol-2-yl]-3-(4-methanesulphonylphenoxy) benzamide, N-(4-cyano-thiazol-2-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(pyridin-2-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(5-methyl-iso thiazol-3-yl) benzamide, 5-(3-hydroxy-cyclopentyl oxy)-3-(4-methanesulphonylphenoxy)-N-(thiazol-2-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(5-methoxy-thiazol-2-yl) benzamide, 5-(1-hydroxymethyl-2-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(thiazol-2-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(1H-[1,2,3] triazol-4-yl) benzamide, N-(1-acetyl-1H-pyrazol-3-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(pyrazol-3-yl) benzamide, N-(5,6-dihydro-4H-cyclopenta thiazol-2-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy) benzamide, 5-(1-hydroxymethyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(thieno [3,2-d] thiazol-2-yl) benzamide, 3-(3-fluoro-4-methanesulphonylphenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(4-methanesulphonylphenoxy)-5-(2-methoxy-1-methyl-ethoxy)-N-(pyrazol-3-yl) benzamide, 3-(4-cyano-phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(4-ethylsulfonyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(3-hydroxy-1-methyl-propoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(4-ethane sulfonyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-isopropyl sulfonyl phenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(4-hydroxy-4-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta thiazol-2-yl)-3-(4-methanesulphonylphenoxy) benzamide, 3-(4-dimethylcarbamoyl-phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(4-acetyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(1,3,4-thiadiazol-2-yl sulphanyl) benzamide, N-(1-ethyl-1H-pyrazol-3-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonylphenoxy) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methanesulphonyl pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methoxycarbonylamino methyl-phenoxy)-N-(3-methyl-1,2,4-thiadiazol-5-yl) benzamide, 5-(1-hydroxymethyl-propoxy)-3-(6-methanesulphonyl pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-methanesulphonyl pyridin-3-yloxy)-5-(1-methoxymethyl-

propoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-isopropoxy-3-(6-methanesulphonyl pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonyl pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl phenyl sulphanyl)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-cyclopropyl oxy-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-methanesulphonyl pyridin-3-yloxy)-5-(1-methoxymethyl-propoxy)-N-(pyrazol-3-yl) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(1-hydroxymethyl-propoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(6-ethane sulfonyl pyridin-3-yloxy)-3-(2-methoxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 2-[3-(4-methanesulphonylphenoxy)-5-(1-methyl-1H-pyrazol-3-yl carbamoyl)-phenoxy] propionic acid tert-butyl ester, 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(2-methoxy-1-methyl-ethoxy)-N-(pyrazol-3-yl)-benzamide, 3-(6-methanesulphonyl pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl)-5-(tetrahydrofuran-3-yl) benzamide, N-(1-ethyl-1H-pyrazol-3-yl)-5-(2-hydroxy-1-methyl-ethoxy)-3-(6-methanesulphonyl pyridin-3-yloxy) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonyl pyridin-3-yloxy)-N-(pyrazol-3-yl) benzamide, 3-(6-methanesulphonyl pyridin-3-yloxy)-5-(2-methoxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(2-fluoro-1-fluoromethyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 2-[3-(4-methanesulphonylphenoxy)-5-(1-methyl-1H-pyrazol-3-yl carbamoyl)-phenoxy] propionic acid, 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-isopropoxy-N-(pyrazol-3-yl) benzamide, 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-isopropoxy-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(pyrazol-3-yl) benzamide, 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(pyridin-2-yl) benzamide, 3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-thiazol-2-yl-benzamide, 5-(2-fluoro-1-methyl-ethoxy)-3-(6-methanesulphonyl pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-chloro-1-methyl-ethoxy)-3-(6-ethane sulfonyl pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-N-(isoxazol-3-yl)-3-(6-methanesulphonyl pyridin-3-yloxy) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonyl pyridin-3-yloxy)-N-(pyridin-2-yl) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonyl pyridin-3-yloxy)-N-(3-methyl-[1,2,4]-thiadiazol-5-yl) benzamide, 3-(4-dimethyl sulphamoyl phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(3-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-3-(6-isopropyl sulfonyl pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 3-(3-chloro-4-methanesulphonylphenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(1-

methyl-1H-pyrazol-3-yl)-3-(pyridin-3-yloxy) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(pyridin-3-yloxy) benzamide, 5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(pyridin-4-yloxy) benzamide, 5-(2-fluoro-1-fluoromethyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl)-3-(pyridin-4-yloxy) benzamide, 2-[3-(6-ethane sulfonyl pyridin-3-yloxy)-5-(1-methyl-1H-pyrazol-3-yl carbamoyl)-phenoxy] propionic acid, 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(3-fluoro-4-methanesulphonylphenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide, or pharmacologically acceptable salts thereof.

16. A compound which is 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl-phenoxy)-N-thiazol-2-yl-benzamide or pharmacologically acceptable salts thereof.

17. A compound which is N-(4-hydroxymethyl-thiazol-2-yl)-3-(4-methanesulphonyl-phenoxy)-5-(1-methoxymethyl-propoxy)-benzamide or pharmacologically acceptable salts thereof.

18. A compound which is 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl-phenoxy)-N-pyridin-2-yl-benzamide or pharmacologically acceptable salts thereof.

19. A compound which is 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl-phenoxy)-N-(2-methylthiazol-4-yl)-benzamide or pharmacologically acceptable salts thereof.

20. A compound which is 5-(2-hydroxy-1-methyl-ethoxy)-3-([1,3,4] thiadiazol-2-yl sulphanyl)-N-thiazol-2-yl-benzamide or pharmacologically acceptable salts thereof.

21. A compound which is 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl-phenoxy)-N-(3-methyl-[1,2,4]-thiadiazol-5-yl)-benzamide or pharmacologically acceptable salts thereof.

22. A compound which is 5-(2-hydroxy-1-methyl-ethoxy)-3-(4-methanesulphonyl-phenoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide or pharmacologically acceptable salts thereof.

23. A compound which is 3-(3-fluoro-4-methanesulphonyl-phenoxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide or pharmacologically acceptable salts thereof.

24. A compound which is 3-(6-ethane sulfonyl-pyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide or pharmacologically acceptable salts thereof.

25. A compound which is 3-(6-ethane sulfonyl-pyridin-3-yloxy)-5-isopropoxy-N-(1-methyl-1H-pyrazol-3-yl) benzamide or pharmacologically acceptable salts thereof.

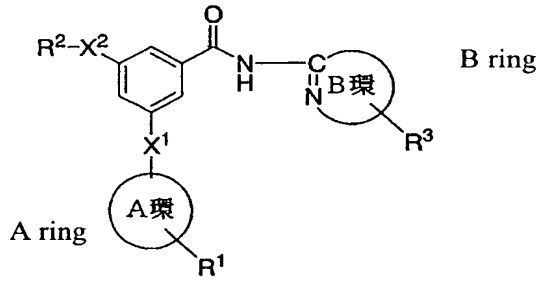
26. A compound which is 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonyl-pyridin-3-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) benzamide or pharmacologically acceptable salts thereof.

27. A compound which is 3-(6-ethane sulfonyl-pyridin-3-yloxy)-5-(2-hydroxy-1-methyl-ethoxy)-N-(isoxazol-3-yl) benzamide or pharmacologically acceptable salts thereof.

28. A compound which is 5-(2-fluoro-1-fluoromethyl-ethoxy)-3-(6-methanesulphonyl-pyridin-3-yloxy)-N-(pyrazol-3-yl) benzamide or pharmacologically acceptable salts thereof.

29. A medicinal composition which is formed from the following (1) to (3) to be used for treatment prevention and/or delaying the development of type II diabetes.

(1). The compound which is represented by formula (I).



(I)

(each symbol is the same as above)

(2). One or more compounds selected from the group comprising following (a)-(g).

(a) Other glucokinase activator.

(b) Bisguanide.

(c) PPAR agonist.

(d) Insulin.

(e) Somatostatin.

(f) α-glucosidase inhibitor, and

(g) Insulin secretion promoter.

(3). Pharmacologically acceptable carriers.

30. A glucokinase activator, wherein the effective ingredient comprises the compound in accordance with any of Claims 1 to 28.

31. An agent for preventing and/or treating diabetes, wherein the effective ingredient comprises the compound in accordance with any of Claims 1 to 28.

32. An agent for prevention and/or therapy of obesity, wherein the effective ingredient comprises the compound in accordance with any of Claims 1 to 28.

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